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(54) Title: MODULATORS OF ACETYLCHOLINE RECEPTORS

(57) Abstract: The present invention relates to compounds that modulate neurotransmission by promoting the release of neurotransmitters such as acetylcholine, dopamine and norepinephrine. More particularly, the present invention relates to thio-bridged aryl compounds that are capable of modulating acetylcholine receptors and pharmaceutical compositions comprising such compounds. The compounds disclosed are useful for the treatment of dysfunctions of the central and autonomic nervous systems.

WO 03/062235 A1

MODULATORS OF ACETYLCHOLINE RECEPTORS

The present invention relates to compounds that modulate neurotransmission by promoting the release of neurotransmitters such as acetylcholine, dopamine and norepinephrine. More particularly, the present invention relates to thio-bridged aryl compounds that are capable of modulating acetylcholine receptors and pharmaceutical compositions comprising such compounds.

Acetylcholine receptors modulate the release of neurotransmitters such as for example dopamine, norepinephrine, acetylcholine, and serotonin from different brain regions. By such action, acetylcholine receptors participate in the modulation of neuroendocrine function, respiration, mood, motor control and function, focus and attention, concentration, memory and cognition, and the mechanisms of substance abuse. Ligands for acetylcholine receptors have been demonstrated to have effects on attention, cognition, appetite, substance abuse, memory, extrapyramidal function, cardiovascular function, pain, and gastrointestinal motility and function. The distribution of acetylcholine receptors that bind nicotine, i.e., nicotinic acetylcholine receptors, is widespread in the brain, including being found in the basal ganglia, limbic system, cerebral cortex and mid- and hind-brain nuclei. In the periphery, their distribution includes being in muscle, autonomic ganglia, the gastrointestinal tract and the cardiovascular system.

Acetylcholine receptors have been shown to be decreased in the brains of patients suffering from Alzheimer's disease or Parkinson's disease, diseases associated with dementia, motor dysfunction and cognitive impairment. Such correlations between acetylcholine receptors and nervous system disorders suggest that compounds that modulate acetylcholine receptors will have beneficial therapeutic effects for many human nervous system disorders. Thus, there is a continuing need for compounds that can modulate the activity of acetylcholine receptors.

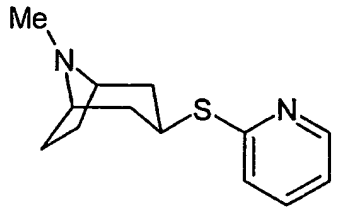
Nicotinic acetylcholine receptors (nAChRs) belong to the ligand gated ion channel family of neurotransmitter receptors. In neuronal and peripheral tissue, nAChRs possess a pentameric structure consisting of 5 protein subunits surrounding a central ion channel. Five neuromuscular subunits (α, β, γ, δ, ε), ten peripheral or neuronal α-subunits (α1 to α10), and three peripheral or neuronal β-subunits (β2 to β4) have been identified. These subunits combine to form pentameric receptors in three ways: first, with homomeric 5[α] stoichiometry, for example, α7 to α9; second, with heteromeric 2[α]3[β] stoichiometry, for example, combinations of α1 to α6 and β2 to β4 subunits; and third, the 2[α]1[β]1[δ]1[γ/ε] stoichiometry found in neuromuscular receptors.

Nicotine modulates multiple neuronal, peripheral and neuromuscular subtypes of nAChRs. While demonstrating beneficial effects in a number of neuronal diseases mediated by nAChRs, nicotine also demonstrates a number of undesirable side effects on cardiovascular, gastrointestinal and neuromuscular systems. It will be appreciated that there is a need for compounds that can selectively modulate a single or specific group of nAChRs.

It is desired to provide new compounds which selectively modulate the activity of acetylcholine receptors. In particular, it is desired to provide compounds that are capable of acting as selective modulators, preferably agonists, of beta 4 subtype nicotinic acetylcholine receptors. It is also desirable to provide a method of treatment of dysfunctions of the central and peripheral nervous systems to treat, for example, dementia, cognitive and conduct disorders including attention deficit hyperactivity disorder, neurodegenerative disorders, including Alzheimers disease, Parkinson's disease and other diseases in which degeneration leads to impaired functioning of the sensory or motor systems, extrapyramidal disorders associated with neuroleptic use, convulsive disorders, epilepsy, cardiovascular disorders, endocrine disorders, psychotic disorders including schizophrenia and related disorders, bipolar disease and obsessive-compulsive disorder, eating disorders, sleep-related disorders, affective disorders including depression, anxiety, panic states and stress-related disorders, aggression, emesis, pain and hyperalgesic states of inflammatory and neuropathic origins, sleep and sexual disorders

and alcohol and drug abuse or states associated with drug withdrawal including smoking cessation.

WO97/19059 discloses substituted aryl compounds capable of modulating acetylcholine receptors. WO99/32117 discloses similar compounds wherein the aryl moiety is replaced by a 2- or 4-pyridine moiety. Specifically, it discloses the compound

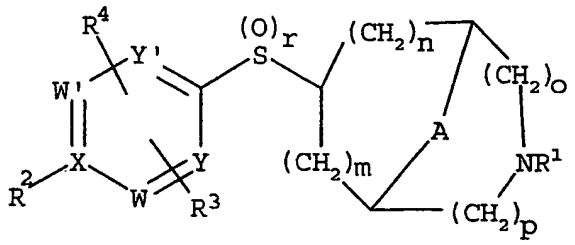


Other compounds specifically disclosed all possess a linker, usually methylene or ethylene, between the S atom and either (or both) of the two ring systems shown above. It would be desirable to provide alternative compounds to those disclosed in WO97/19059 and WO99/32117. Preferably, such alternatives should exhibit one or more of the following advantages: improved binding to nAChRs, greater modulation of nAChRs, improved selectivity between different nAChRs and improved pharmacokinetic properties (e.g. improved bioavailability).

Radl et al (Archiv der Pharmazie, Weinheim, Germany, 2000, 333(5), 107-112) discloses the synthesis and analgesic activity of some side-chain modified anpirtoline derivatives including 3-(3-chlorophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane and 2-chloro-6-(3-(8-methyl-8-azabicyclo[3.2.1]octyl)thio)-pyridine.

EP0398578 discloses 3-phenylthio-8-azabicyclo[3.2.1]octane and 3-phenylthio-8-methyl-8-azabicyclo[3.2.1]octane as intermediates in the synthesis of piperidino and 8-azabicyclo[3.2.1]oct-8-yl alkanols which are useful for the treatment of CNS disorders.

The present invention provides compounds represented by Formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is -H,

-OH,

$-NH_2$,

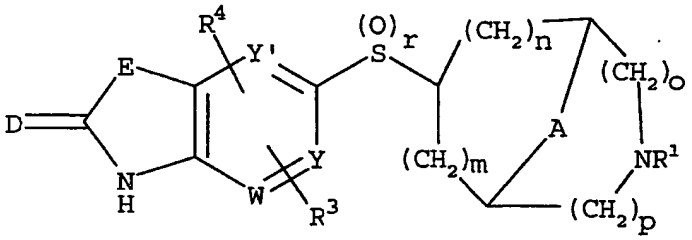
-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or $-SO_2-$;
V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -$C(O)OC_{1-4}$alkyl, $-OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and
T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent,

aryl,

$-(L)_a-Z$, wherein L is CH_2, CO, O, NH or N(C_{1-4}alkyl) and a is 0 or 1;
and
Z is C_{1-3}alkyl-F, C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{0-3}alkyl-SO_2-R^6, C_{0-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6, C_{1-3}alkyl-CN or C_{1-3}alkyl-

NR^6_2, wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)

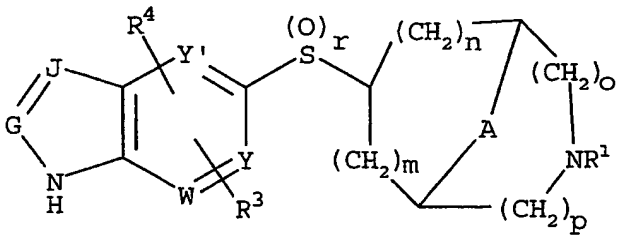


(Ia)

wherein D is O or S; and

E is O, S, NR^5, $C(R^5)_2$, O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-O, CR^5_2-$S(O)_r$, CR^5_2-NR^5, CR^5_2-CR^5_2, CO-NR^5, or CR^5=CR^5; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib)



Formula (Ib)

wherein G is CR^5 or N; and

J is CR^5 or N;

unless X is N in which case R^2 is absent

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

R^6 is each independently H, C_{1-6}alkyl, aryl or arylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms;

X is C or N;

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m, n, o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

provided that

when X, W, W', Y and Y' are all C, R^3 is H, R^4 is H or Cl positioned *meta* to the sulphur atom, A is $(CH_2)_q$ and R^1 is selected from H, unsubstituted C_{1-4}alkyl and unsubstituted C_{3-4}cycloalkyl; then R^2 may not be H or –OH,

and that

when one of X, Y and Y' is N, R^3 is H, R^4 is H or Cl positioned *meta* to the sulphur atom, A is $(CH_2)_q$ and R^1 is selected from H, unsubstituted C_{1-4}alkyl and unsubstituted C_{3-4}cycloalkyl; then R^2 may not be H or –OH.

In a further embodiment of the present invention:

R^2 is -H,

-NH_2,

-NH-Q-V-T as defined in claim 1,

aryl,

-$(L)_a$-Z as defined in claim 1,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;
unless X is N in which case R^2 is absent.

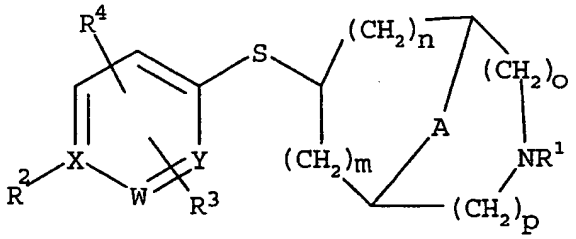
In a further embodiment of the present invention:

R^2 is -NH-Q-V-T as defined in claim 1,
aryl,
$-(L)_a-Z$ as defined in claim 1,
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;
unless X is N in which case R^2 is absent.

In a further embodiment of the present invention:

R^2 is -NH-Q-V-T wherein Q is -C(O)-NH-, or -C(O)O-;
V is as defined in claim 1; and
T is as defined in claim 1;
aryl,
$-(L)_a-Z$ as defined in claim 1,
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or
linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;
unless X is N in which case R^2 is absent.

In one embodiment, the present invention provides a sub-group of compounds (Group A) represented by formula (II) or pharmaceutically acceptable salts thereof:



(II)

wherein:

R^1 is -H; or

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio; or

aryl-C_{1-4}alkyl

R^2 is –H;

–OH;

$-NH_2$;

-NH-Q-V-T

Q is -C(O)-;

-C(O)-NH-;

-C(O)O-; or

$-SO_2-$

V is aryl;

aryl-C_{1-12}alkyl;

diaryl-C_{1-12}alkyl;

lactonyl; or

C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -C(O)OC_{1-4}alkyl, -OC(O)C_{1-4}alkyl, aryl-C_{1-4}alkoxy, aryloxy, SO_2C_{1-4}alkyl;

T is H;

halogen;

aryl;

aryl-C_{1-4}alkyl; or

aryloxy;

unless X is N in which case R^2 is absent

R^3 and R^4 are each independently selected from H, halogen, C_{1-4}alkyl, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, -C_{1-4}alkyl-OH;

X is C or N;

W is C or N, provided that both X and Y are not N;

Y is C or N

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$

m,n,o and p are independently 0, 1, 2 or 3

q is optionally 1, 2 or 3.

Within Group A, A is preferably a double bond or $(CH_2)_q$ and R^1 is preferably -H; or C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio; or aryl-C_{1-4}alkyl.

Within Group A, R^1 is more preferably H; C_{1-6}alkyl optionally substituted with 1 or 2 hydroxyl groups; or aryl-C_{1-4}alkyl. When R^1 is an aryl-C_{1-4}alkyl group, examples of suitable groups are benzyl, p-methoxybenzyl, furanylmethyl, imidazolylmethyl, pyridinylmethyl, thienylmethyl, pyridylmethyl, N-hydroxypyridylmethyl or thiazolylmethyl.

Within Group A, R^1 is more preferably H, methyl, cyclopropylmethyl, 2-hydroxyethyl or isobutyl. When R^1 is one of these groups, greater potency is generally observed. More preferably, R^1 is a methyl group.

In one embodiment of Group A, R^2 is H. When R^2 is H, R^3 is preferably carbonamido (-$CONH_2$) or –C_{1-4}alkyl-OH and R^4 is H, C_{1-4}alkyl, CF_3, halogen or cyano (more preferably H, halogen or cyano). More preferably R^3 is carbonamido (-$CONH_2$) or –C_{1-4}alkyl-OH and R^4 is methyl, CF_3, Cl or cyano (more preferably Cl or cyano).

In another embodiment of Group A, R^2 is OH. When R^2 is OH, R^3 and R^4 are preferably H, C_{1-4}alkyl, CF_3, cyano or halogen (more preferably H, cyano or halogen). More

preferably R^3 is methyl, CF_3, Cl or cyano (more preferably Cl or cyano) attached to position Y when Y is C.

Generally, within Group A, when R^2 is of formula –NH-Q-V-T, T is preferably H and R^3 and R^4 are preferably H, methyl, CF_3, chloro- or cyano (more preferably H, chloro- or cyano).

In another embodiment of Group A, R^2 is of the formula –NH-SO_2-V-T, wherein V is aryl, -C_{1-12}alkyl or aryl-C_{1-12}alkyl. In this embodiment of the present invention R^3 is preferably H, methyl, CF_3, Cl or cyano (more preferably H, Cl or cyano) and R^4 is preferably H.

Within Group A, when R^2 is of formula –NH-SO_2-V-T, preferably V is selected from C_{1-12}alkyl, phenyl, naphthyl, thienyl, oxazolyl, isoxazolyl, or phenyl(CH=CH)–, optionally substituted with 1, 2, 3 or 4 substituents selected from:

-NO_2;
halogen;
-CF_3;
C_{1-12}alkoxy;
C_{1-12}alkylthio;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
-OCF_3;
-C(O)OC_{1-4}alkyl;
-OCH_2CF_3;
-NHC(O) C_{1-4}alkyl.

Within Group A, when R^2 is of formula –NH-SO_2-V-T, preferably T is selected from H, or diazole, oxazole, isoxazole, phenyl or phenoxy, optionally substituted with 1, 2, 3 or 4 substituents selected from

-NO_2;

halogen;

$-CF_3$;

C_{1-12}alkoxy;

C_{1-12}alkylthio;

C_{1-12}alkyl;

C_{1-4}alkylsulfonyl;

-CN;

$-OCF_3$;

$-C(O)OC_{1-4}$alkyl;

$-OCH_2CF_3$;

$-NHC(O)C_{1-4}$alkyl.

Within Group A, when R^2 is of formula $-NH-SO_2-V-T$, V is more preferably selected from 3-chloro-4-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-yl, 2,5,6-trimethyl-4-methoxyphenyl, 4-methoxyphenyl, 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl (even more preferably selected from 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-yl, 2,5,6-trimethyl-4-methoxyphenyl, 4-methoxyphenyl, 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl) and T is preferably H.

In a further embodiment within Group A, when R^2 is of formula $-NH-SO_2-V-T$, T is preferably 2-chloro-5-nitrophenoxy and V is preferably phenyl.

In an alternative embodiment of Group A, R^2 is of formula $-NH-C(O)-V-T$ wherein V is selected from

aryl;

aryl-C_{1-12}alkyl;

diaryl-C_{1-12}alkyl;

lactonyl; or

C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy, aryloxy. In this embodiment of the present invention, R^3 is preferably H, methyl, CF_3, Cl or cyano (more preferably H, Cl or cyano) and R^4 is H.

When R^2 is of formula –NH-C(O)-V-T, preferably V is selected from C_{1-12}alkyl, phenyl, phenyl-C_{1-12}alkyl, diphenylmethyl, naphthyl, furanyl, thienyl, diazolyl, pyridinyl, thiazolyl, benzothienyl, fluorenyl, oxazolyl or isoxazolyl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkoxy;
C_{1-12}alkylthio;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl;
$-OCH_2CF_3$.

When R^2 is of formula –NH-C(O)-V-T, more preferably V is C_{1-12}alkyl.

When R^2 is of formula –NH-C(O)-V-T, preferably T is selected from

H;
halogen; or
diazole, oxazole, isoxazole, phenyl, phenoxy or benzodioxanyl optionally substituted with 1, 2, 3 or 4 substituents selected from
$-NO_2$;
halogen;
$-CF_3$;
C_{1-12} alkylthio;

C_{1-12} alkoxy;
C_{1-12} alkyl;
C_{1-4} alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$ alkyl.

When R^2 is of formula –NH-C(O)-V-T, more preferably T is H.

In an alternative embodiment of Group A, R^2 is of formula –NH-C(O)NH-V-T wherein V is selected from

C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy or aryloxy;
aryl; or
aryl-C_{1-12}alkyl.

When R^2 is of formula –NH-C(O)NH-V-T, preferably V is selected from phenyl, phenyl-C_{1-12}alkyl or naphthyl optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkylthio;
C_{1-12}alkoxy;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl.

When R^2 is of formula –NH-C(O)NH-V-T, preferably T is H.

In an alternative embodiment of Group A, R^2 is of formula –NH-C(O)O-V-T, wherein V is selected from

C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy or aryloxy;

aryl; or

aryl-C_{1-12} alkyl.

When R^2 is of formula –NH-C(O)O-V-T, preferably V is selected from phenyl or phenyl-C_{1-12}alkyl optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;

halogen;

$-CF_3$;

C_{1-12}alkylthio;

C_{1-12}alkoxy;

C_{1-12}alkyl;

C_{1-4}alkylsulfonyl;

-CN;

$-OCF_3$;

$-C(O)O-C_{1-4}$alkyl; or

$-OCH_2CF_3$.

When R^2 is of formula –NH-C(O)O-V-T, preferably T is H.

In another embodiment, the present invention provides a further sub-group of compounds (Group B) represented by formula (I) or pharmaceutically acceptable salts thereof:

wherein R^2 is of formula –NH-C(O)-V-T

wherein V is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl or aryl-C_{1-12}alkyl; and

T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent.

In a preferred embodiment within Group B, when V is H, C_{1-6}alkyl or C_{3-6}cycloalkyl, preferably T is H unless V is H in which case T is absent.

In another preferred embodiment within Group B, when V is aryl or aryl-C_{1-12}alkyl, preferably T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy.

More preferably, V is phenyl, pyridyl, thienyl, thiazolyl, thiadiazolyl, or phenyl-C_{1-6}alkyl; and T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy.

In another embodiment, the present invention provides a further sub-group of compounds (Group C) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein

R^1 is -H,
C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is -NH_2, or
-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO_2-;
V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -C(O)OC_{1-4}alkyl, -OC(O)C_{1-4}alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and
T is H, halogen, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

X is C;

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are not more than two N atoms in the aryl ring and provided that at least one of W, W', Y or Y' is N;

A is optionally a CH=CH double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m, n, o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

In a preferred embodiment of the compounds of Group C only one of W, W', Y and Y' is N.

In one embodiment of the compounds of Group C

W is C;

W' is C;

Y' is C; and

Y is N.

In another embodiment of the compounds of Group C

W is N;

W' is C;

Y' is C; and

Y is C.

In another embodiment of the compounds of Group C, R^2 is $-NH_2$.

In another embodiment of the compounds of Group C

R^2 is -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or $-SO_2-$;
V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -$C(O)OC_{1-4}$alkyl, -$OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and

T is H, halogen, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent.

Within Group C, when R^2 is -NH-Q-V-T, preferably Q is -SO_2- or –CO-.

In another embodiment, the present invention provides a further sub-group of compounds (Group D) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein

R^1 is -H,
C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is aryl,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or-C_{1-4}alkyl-OH,

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

X is C,

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a CH=CH double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m, n, o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

Within Group D, R^2 is preferably a C_3 to C_{12} aromatic or heteroaromatic group optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

Within Group D, R^2 is more preferably phenyl, naphthyl, fluorenyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl or carbolinyl optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

Within Group D, R^2 is even more preferably phenyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothienyl, or quinolinyl

optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

Within Group D, R^2 is even more preferably phenyl, pyridyl, or benzofuranyl, optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

In another embodiment, the present invention provides a further sub-group of compounds (Group E) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is $(L)_a$-Z, wherein L is O; CO, CH_2, NH or N(C_{1-4}alkyl) and a is 0 or 1; and

Z is C_{1-3}alkyl-F, C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{0-3}alkyl-SO_2-R^6, C_{0-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6, C_{1-}

$_3$alkyl-CN or C_{1-3}alkyl-NR^6_2 wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^6 is each independently H, C_{1-6}alkyl, aryl, or arylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms;

X is C;

W is C or N,

Y is C or N,

W' is C or N,

Y' is C or N,

provided that there are no more than two N atoms in the aryl ring,

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m, n, o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

In one preferred embodiment of sub-group E, L is CO.

In another preferred embodiment of sub-group E, L is CH_2.

In another preferred embodiment of sub-group E, L is O.

In another preferred embodiment of sub-group E, L is NH or N(C_{1-4}alkyl).

In another preferred embodiment of sub-group E, Z is C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{1-3}alkyl-OR^6 or C_{1-3}alkyl-NR^6_2 wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl.

In another preferred embodiment of sub-group E, Z is C_{0-3}alkyl-aryl-R^6 wherein aryl is selected from phenyl, naphthyl, fluorenyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl or carbolinyl optionally, be substituted with one or more substituents selected from C_1 to C_{12} alkyl (preferably C_1 to C_6 alkyl), C_1 to C_{12} alkoxy (preferably C_1 to C_6 alkoxy), thio, C_1 to C_{12} alkylthio (preferably C_1 to C_6 alkylthio), carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, trihalo(C_1 to C_6 alkoxy), trihalomethoxy, trihalomethyl(C_1 to C_6 alkyl), hydroxy, hydroxy(C_1 to C_6)alkyl, (C_1 to C_6 alkoxy)carbonyl, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aminocarboxy, C_1 to C_6 alkylaminocarboxy, di(C_1 to C_6 alkyl)aminocarboxy, aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylaminocarboxy(C_1 to C_6)alkyl, di(C_1 to C_6 alkyl)aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylcarbonylamino, C_1 to C_6 alkylcarbonyl(C_1 to C_6 alkyl)amino, halo, C_1 to C_6 alkylhalo, sulphamoyl, tetrazolyl and cyano and wherein each C_{0-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

In another preferred embodiment of sub-group E, Z is C_{1-3}alkyl-CO-NR^6_2, wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

In another preferred embodiment of sub-group E, Z is C_{1-3}alkyl-CO_2-R^6, wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

In another preferred embodiment of sub-group E, Z is C_{1-3}alkyl-OR^6 wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

In another preferred embodiment of sub-group E, Z is C_{1-3}alkyl-NR^6_2 wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

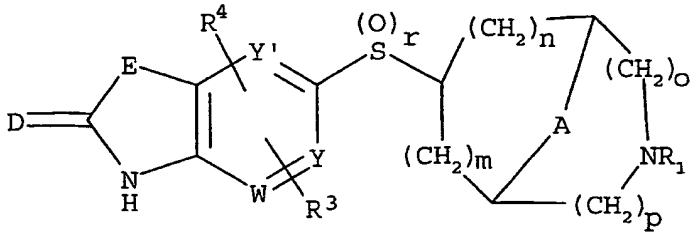
Preferably, within Group E, R^6 is/are each independently H, C_{1-6}alkyl, phenyl, or phenylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms. More preferably, within Group E, R^6 is/are each independently H, methyl, ethyl, propyl, cyclohexyl, or benzyl, each of which (except H) may be optionally substituted with 1, 2 or 3 fluorine atoms.

In another embodiment, the present invention provides a further sub-group of compounds (Group F^1) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



(Ia)

wherein D is O or S; and

E is O, S, NR^5, or $C(R^5)_2$,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring,

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

In one preferred embodiment of sub-group F^1, E is O or NR^5.

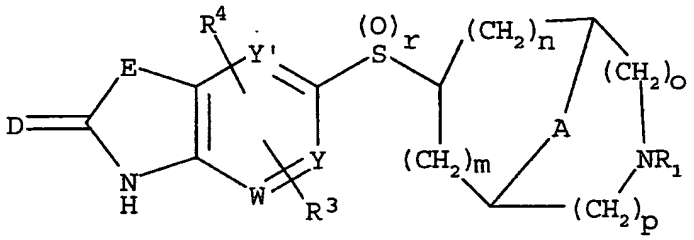
In another preferred embodiment of sub-group F^1, R^5 is/are each independently H or C_{1-4}alkyl.

In another embodiment, the present invention provides a further sub-group of compounds (Group F^2) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



(Ia)

wherein D is O or S; and

E is O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-O, CR^5_2-$S(O)_r$, CR^5_2-NR^5, CR^5_2-CR^5_2, CO-NR^5, or CR^5=CR^5;

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H, C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond or $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

In one preferred embodiment of sub-group F^2, E is O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-CR^5_2, or CR^5=CR^5. More preferably, E is O-CR^5_2, NR^5-CO, or CR^5=CR^5.

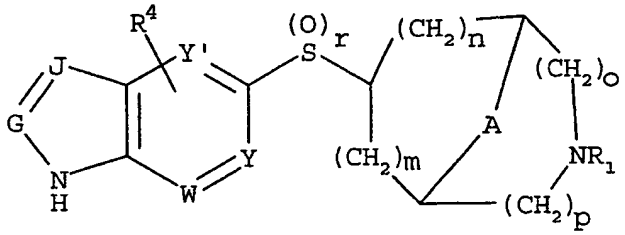
In another preferred embodiment of sub-group F^2, R^5 is/are each independently H or C_{1-4}alkyl.

In another embodiment, the present invention provides a further sub-group of compounds (Group G) represented by formula (I) or pharmaceutically acceptable salts thereof: wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib)



Formula (Ib)

wherein G is CR^5 or N; and

J is CR^5 or N;

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-}

$_{10}$cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond or $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

In a preferred embodiment of sub-group G, each R^5 is H.

Within Group A, the sum of m, n, o and p is preferably 2. More preferably, m and n are 1; o and p are 0.

Within Group A, q is preferably 2.

Within Group A, X, Y and Z are preferably C.

For all embodiments of the present invention (except Group A, for which r is 0) r is preferably 0 or 2, and most preferably 0.

For all embodiments of the present invention, R^1 is preferably H or C_{1-3}alkyl, more preferably methyl.

For all embodiments of the present invention, A is preferably CH_2, CH_2CH_2 or CH=CH. More preferably, for all embodiments A is CH_2CH_2. Also preferred, for all embodiments is when A is CH=CH.

For all embodiments of the present invention, the sum of m, n, o and p is preferably 2. More preferably, m and n are 1; o and p are 0.

For all embodiments of the present invention it is preferred that m and n are 1, o and p are 0 and A is CH_2CH_2 or CH=CH.

For all embodiments of the present invention, R^3 is preferably H, halogen, C_{1-4}alkyl, cyano, CF_3, or OC_{1-4}alkyl, and R^4 is preferably H, halogen, C_{1-4}alkyl, cyano, CF_3, or OC_{1-4}alkyl.

For all embodiments of the present invention, one or both of R^3 and R^4 are preferably positioned ortho to the $S(O)_r$ moeity.

For all embodiments of the present invention, one or both of R^3 and R^4 are preferably halogen, C_{1-4}alkyl, cyano, CF_3, or OC_{1-4}alkyl, more preferably halogen, cyano, or C_{1-4}alkyl, most preferably halogen, positioned ortho to the $S(O)_r$ moeity.

As used herein, the term "alkyl" means a branched or unbranched, cyclic and/or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl), monovalent or divalent hydrocarbyl radical. Examples of branched alkyl groups are isopropyl, isobutyl, tert-butyl etc. Examples of cyclic alkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cycohexyl, adamantyl etc. Examples of groups containing both cyclic and acyclic alkyl moieties are cyclopropylmethyl, cyclohexylpropyl, adamantylethyl etc.

As used herein, the term "aryl" means a C_3 to C_{26}, preferably C_3 to C_{12} aromatic or heteroaromatic group which may, optionally, be substituted with one or more substituents. Aryl substituents are preferably selected from C_1 to C_{12} alkyl (preferably C_1 to C_6 alkyl), C_1 to C_{12} alkoxy (preferably C_1 to C_6 alkoxy), thio, C_1 to C_{12} alkylthio (preferably C_1 to

C_6 alkylthio), carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, trihalo(C_1 to C_6 alkoxy), trihalomethoxy, trihalomethyl(C_1 to C_6 alkyl), hydroxy, hydroxy(C_1 to C_6)alkyl, (C_1 to C_6 alkoxy)carbonyl, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aminocarboxy, C_1 to C_6 alkylaminocarboxy, di(C_1 to C_6 alkyl)aminocarboxy, aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylaminocarboxy(C_1 to C_6)alkyl, di(C_1 to C_6 alkyl)aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylcarbonylamino, C_1 to C_6 alkylcarbonyl(C_1 to C_6 alkyl)amino, halo, C_1 to C_6 alkylhalo, sulphamoyl, tetrazolyl and cyano.

Examples of aromatic groups are phenyl, naphthyl, fluorenyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl and carbolinyl.

Terms such as "aryl-C_{1-12} alkyl group" include groups such as benzyl, 4-chlorobenzyl, phenylpropyl, thienylethyl etc. Further, the alkyl moiety in, for example, aryl-C_{1-12} alkyl groups may optionally be substituted with 1, 2 or 3 substituents selected from halogen, hydroxyl, C_{1-4} alkoxy or C_{1-4} alkylthio.

As used herein the term "lactonyl" means any C_{1-18} cyclic ester. The lactonyl group may be monocyclic or polycyclic.

As used herein, the terms "halogen" or "halo" refer to any one of F, Cl, Br or I.

Compounds of Group A wherein

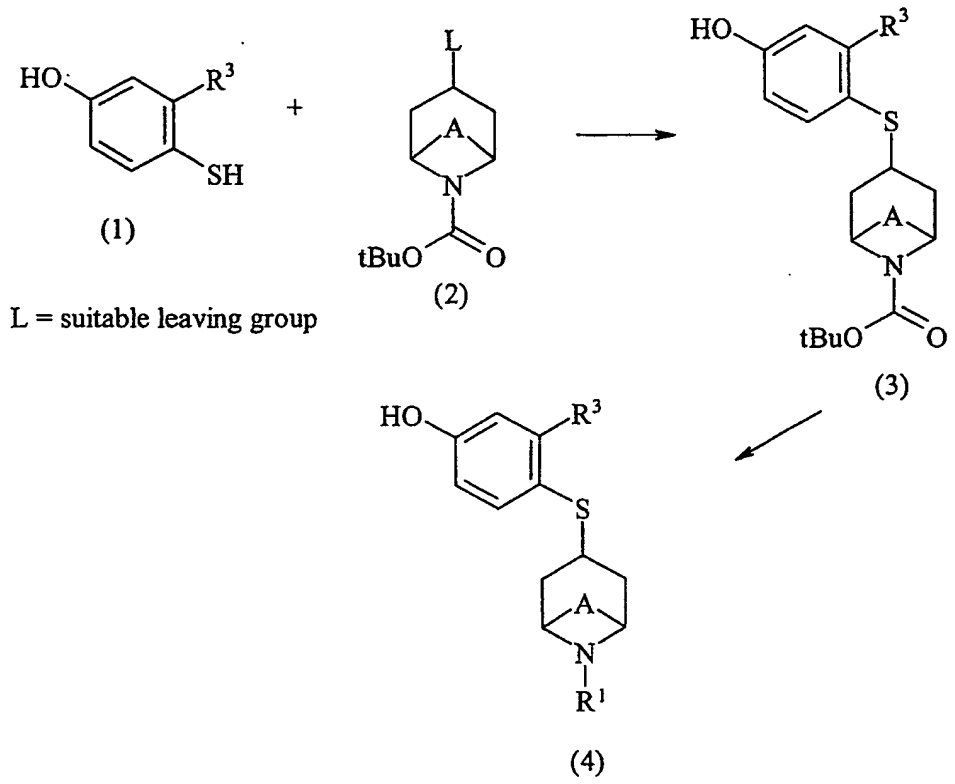
R^2 = OH; and

R^3 = methyl, CF_3, halogen or H;

may be prepared by a procedure exemplified in Reaction Scheme 1.

While Reaction Scheme 1 exemplifies compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 1



Thiophenol (1) [commercial or prepared according to Kita Y.; Takeda, Y.; Okuno, T.; Egi, M.; Ito, K.; Kawaguchi, K; Akai, S. *Chem. Pharm. Bull.* 1997, 45(12), 1887-1890 or Zheng, J.; Hanzlik, R. P. *Drug Metab. Dispos.* 1992, 20(5), 688-694], is coupled with carbamate (2) by displacement of the leaving group L. Suitable leaving groups will be readily apparent to the person skilled in the art. Typical leaving groups include iodo, chloro, bromo, mesyl or tosyl. The coupling reaction is preferably performed in a dipolar solvent such as methanol, THF or DMF. More preferably, the coupling reaction is

performed in a 50/50 mixture of THF and DMF. The coupling reaction is preferably promoted by a suitable base such as potassium hydroxide, sodium hydride, sodium ethoxide, potassium carbonate or DBU. More preferably, the coupling reaction is performed in the presence of potassium carbonate or sodium hydride. Typically the coupling reaction may be carried out over a temperature range of from –78 to 150°C. Preferably, the reaction is carried out at a temperature in the range of from room temperature to 70°C. Reaction times for the coupling reaction are typically from 10 minutes to 24 hours. Preferred reaction times are in the range of 30 minutes to 12 hours.

Thioether (3) is subsequently converted into compounds of the present invention corresponding to the thioether of formula (4). When R^1 is methyl, compounds of formula (4) may be prepared by reduction using, for example, lithium aluminium hydride. When R^1 is other than methyl, compounds of formula (4) may be prepared by deprotection of the carbamate group (usually under acidic conditions) followed by reaction with a suitable aldehyde or allyl halide.

Reduction with lithium aluminium hydride is typically carried out in ether or THF (preferably THF). Preferably, the reduction is carried out at room temperature. Reaction times vary from 10 minutes to up to several days. Preferred reaction times are in the range of 12 to 48 hours.

Alternatively, when R^1 is other than methyl, the carbamate derivative (3) is deprotected under standard conditions. Typical carbamate deprotection conditions involve using either protic acids (e.g. trifluoroacetic acid, HCl, HBr) or Lewis acids (e.g. acid chlorides/bromides, tri(m)ethylsilyl triflate). The solvent used is typically water, dichloromethane, dioxane, THF or ether. Preferably, an acid chloride in dioxane is used when the protecting group is *tert*-butyl carbamate (Boc). Preferably, HBr in water is used when the protecting group is ethyl carbamate. Preferably, deprotection is carried out at room temperature (in the case of Boc-deprotection) or at reflux (in the case of ethyl carbamate).

Once a free amine has been realised following deprotection, procedures for introducing various R^1 groups (wherein R^1 is optionally substituted C_{1-12} alkyl or aryl-C_{1-4} alkyl) will

be readily apparent to the skilled person. Generally, displacement of an alkyl halide (or reductive alkylation with an aldehyde) furnishes the desired tertiary amine (4).

Compounds of Group A wherein:

R^1 = methyl;

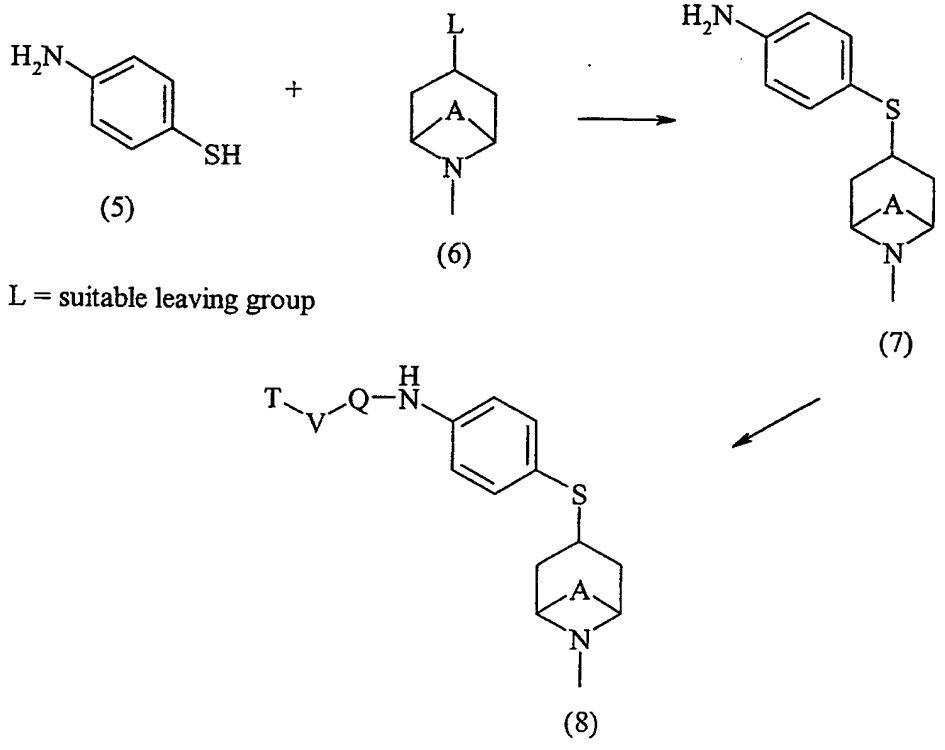
R^2 = $-NH_2$ or -NH-Q-V-T; and

R^3 = H

May be prepared by a procedure exemplified in Reaction Scheme 2.

While Reaction Scheme 2 exemplifies compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 2



L = suitable leaving group

Commercially available 4-aminothiophenol (5) is coupled with amine (6) by displacement of a suitable leaving group L, as outlined above in Reaction Scheme 1. The resultant thioether bridged compound (7) is a key intermediate in the synthesis of compounds of the present invention. It will be readily apparent to the person skilled in the art that various R^2 groups of general type –NH-Q-V-T may be prepared from compound (7) by standard procedures known in the art. For example, when:

(a) Q is -SO_2-, by coupling with a compound of general formula T-V-SO_2-L';

(b) Q is -CO-, by coupling with a compound of general formula T-V-CO-L';

(c) Q is -NH-C(O)-, by coupling with a compound of general formula T-V-N=C=O;

(d) Q is -OC(O) -, by coupling with a compound of general formula T-V-OC(O)-L'

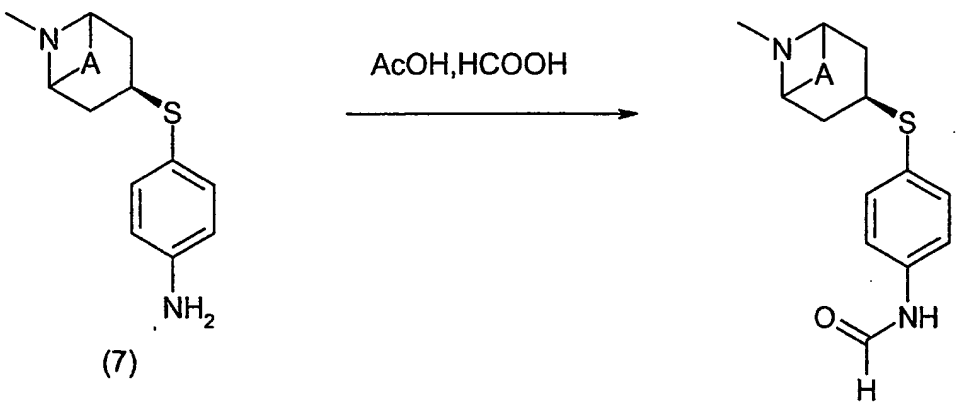
wherein L' is any suitable leaving group, such as Cl, Br, or I.

Typically, the coupling reaction which affords compounds of formula (8) is performed in pyridine or an aprotic solvent such as dichloromethane in the presence of a base such as sodium hydride, pyridine, triethylamine or diisopropylamine. Preferably, the coupling is performed at room temperature with reaction times varying from 10 minutes to 24 hours, preferably 30 minutes to 12 hours.

Compounds of Group B wherein V is H may be prepared by a procedure exemplified in Reaction Scheme 3.

While Reaction Scheme 3 exemplifies compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 3



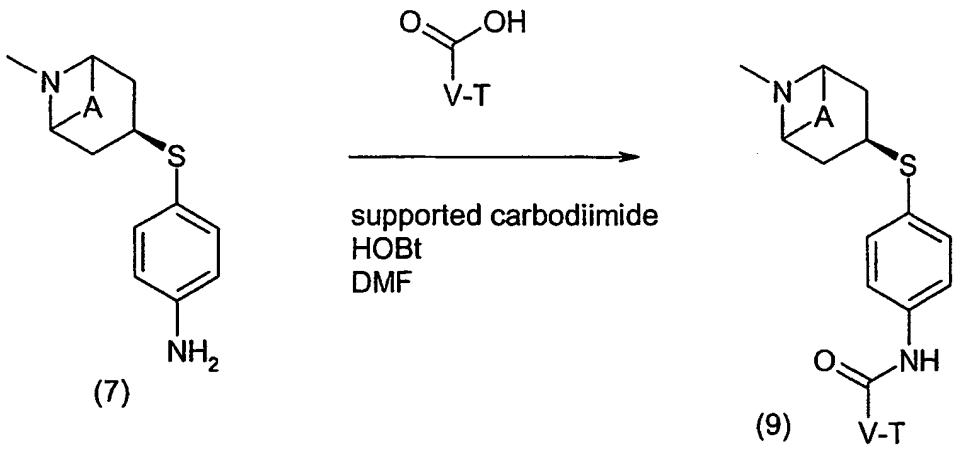
(7)

A mixture of acetic acid and formic acid is heated under reflux for about 2 hours. To this is added the thioether bridged compound (7) (prepared according to Scheme 2 above) and heating continues for about 1.5 hours. The crude mixture may be purified by elution on an SCX cartridge followed by flash chromatography.

Compounds of Group B wherein V is C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl or aryl-C_{1-12}alkyl may be prepared by a procedure exemplified in Reaction Scheme 4.

While Reaction Scheme 4 exemplifies compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 4



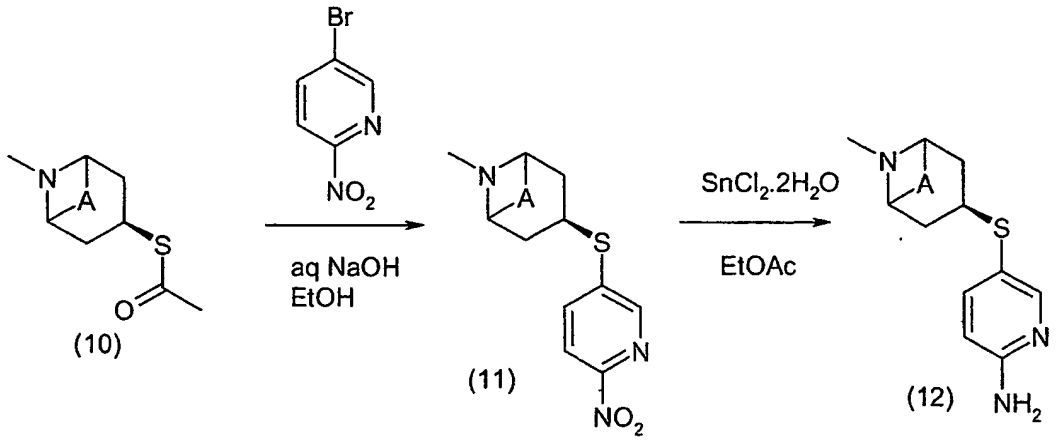
(7) (9)

A mixture of the thioether bridged compound (7) (prepared according to Scheme 2 above), T-V-CO_2H, 1-hydroxybenzotriazole and carbodiimide resin in DMF is stirred at room temperature for about 3 days. The mixture is filtered then passed through an SCX cartridge to provide the product (9).

Compounds of Group C wherein R^2 is NH_2 may be prepared by a procedure exemplified in Reaction Scheme 5.

While Reaction Scheme 5 exemplifies compounds of the present invention wherein m = n = 1, and W is N, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more) or where Y is N.

Reaction Scheme 5



(10) (11) (12)

Step 1:

A mixture of the ethanethioate (10) and 2-nitro-5-bromopyridine in ethanol and aqueous sodium hydroxide is stirred at room temperature for about 18hours. The mixture is applied directly to an SCX cartridge and eluted to yield the crude product which may be purified by preparative LC-MS to provide the nitro-pyridinyl-thio-azabicyclo compound (11).

Step 2:

A mixture of the nitro-pyridinyl-thio-azabicyclo compound (11) and tin (II) chloride dihydrate in ethyl acetate is heated under reflux for about 4 days and then worked up by quenching with aqueous sodium hydrogen carbonate solution to provide the aminopyridine product (12). Step 2 may also be achieved by Pd/C catalysed H_2 reduction

It will be readily apparent to the person skilled in the art that compounds of Group C wherein R^2 is –NH-Q-V-T may be prepared from compound (12) by standard procedures known in the art. For example, when:

(e) Q is -SO_2-, by coupling with a compound of general formula T-V-SO_2-L';

(f) Q is -CO-, by coupling with a compound of general formula T-V-CO-L';

(g) Q is -NH-C(O)-, by coupling with a compound of general formula T-V-N=C=O;

(h) Q is -OC(O) -, by coupling with a compound of general formula T-V-OC(O)-L'

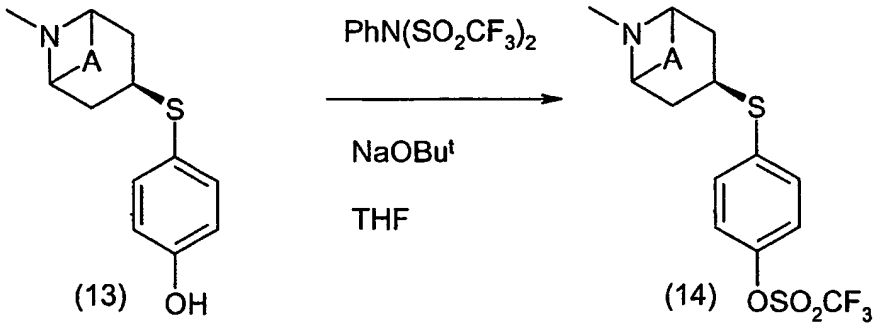
wherein L' is any suitable leaving group, such as Cl, Br, or I.

Compounds of Group D (R^2 is aryl) may be prepared by a procedure exemplified in Reaction Schemes 6 to 9

While Reaction Schemes 6 to 9 exemplify compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 6

Preparation of triflate intermediate:

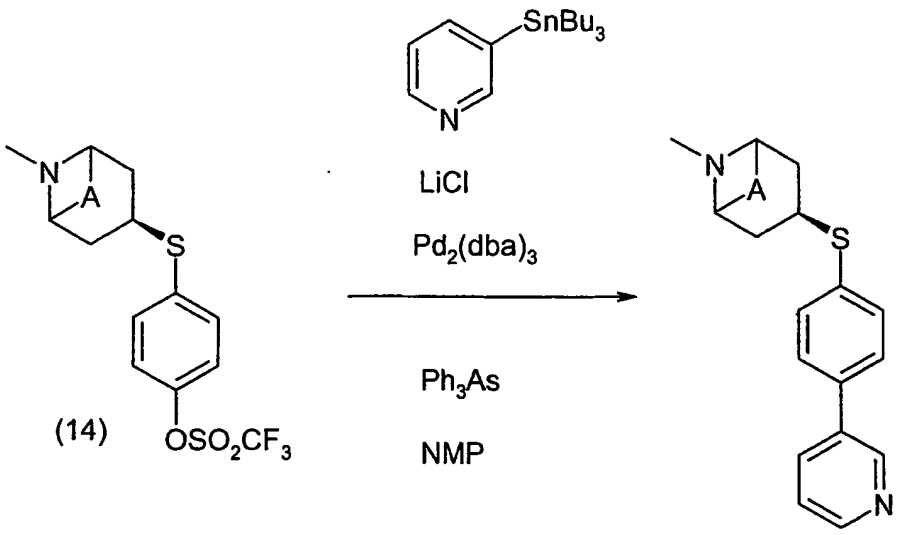


The azabicylothiophenol (13) is dissolved in anhydrous THF under nitrogen and cooled to about 0 °C. To this is added in one portion sodium tert-butoxide and the solution is stirred for 10 minutes. The flask is removed from the ice-bath and N-phenyltrifluoromethanesulfonimide added. The solution is stirred at room temperature for about 16 hours then worked up to provide the triflate intermediate (14).

The triflate intermediate (14) may be used in any of the three procedures shown in Reaction Schemes 7 to 9 below to provide compounds of Group D.

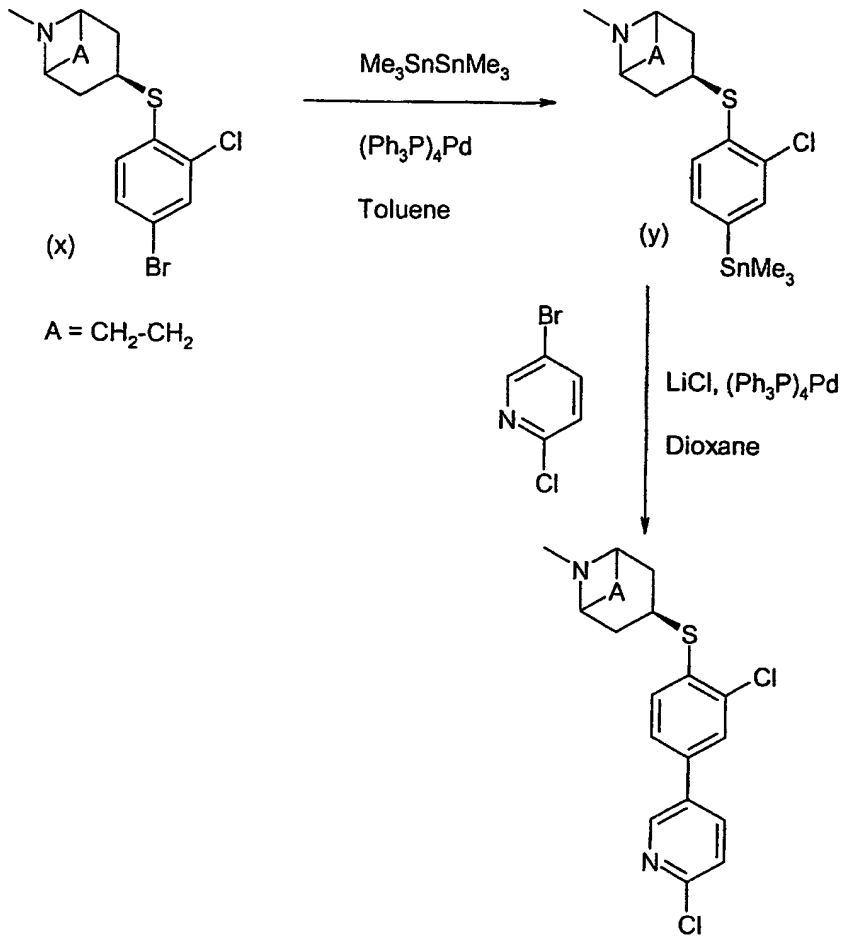
Reaction Scheme 7

Representative example of a Stille coupling:



A mixture of the triflate (14), lithium chloride, triphenylarsine and tris(dibenzylideneacetone)-dipalladium (0) is stirred in N-methylpyrrolidinone under nitrogen. To this is added 3-tributylstannylpyridine and the solution heated to 100 °C. The solution is cooled to room temperature and aqueous sodium hydroxide added to quench the reaction. The mixture is worked up and purified to yield a Group D compound wherein R^2 is pyridinyl.

Representative example of a Stille coupling with microwave assistance



Step 1:

A mixture of 3-[(4-bromo-2-chlorophenyl)thio]-8-methyl-8-azabicyclo[3.2.1]octane (x) (670 mg), hexamethylditin (696 mg) and tetrakis(triphenylphosphine) palladium (0) (112 mg) in dry toluene (5 ml) under nitrogen is subjected to microwave irradiation (200W, 110 °C) in a sealed vessel. After evaporation, the crude material was purified on an Isco CombiFlash device to yield 3-{[2-chloro-4-(trimethylstannyl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane (570 mg).

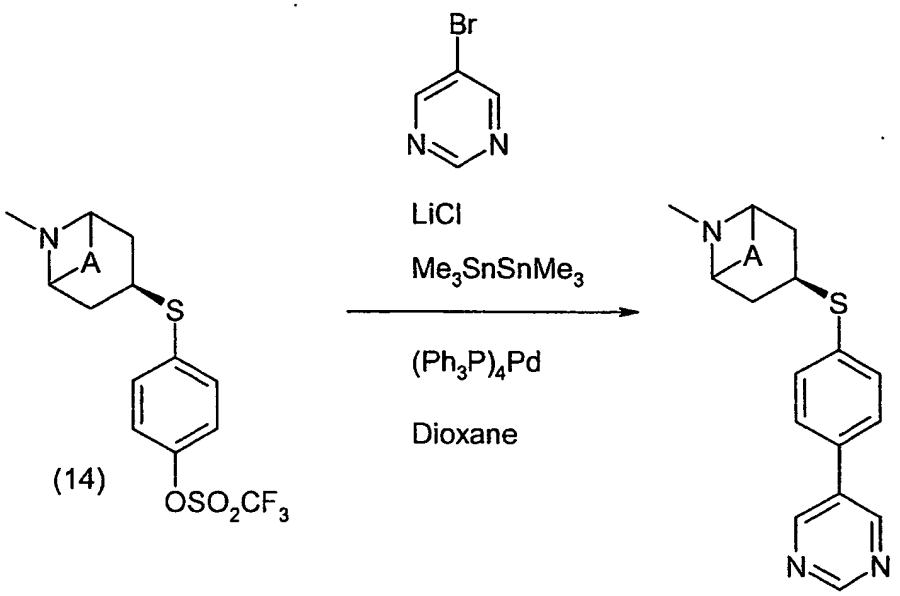
Step 2:

A mixture of 3-{[2-chloro-4-(trimethylstannyl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane (y) (153 mg), 2-chloro-5-bromopyridine (67 mg), lithium chloride (45 mg) and tetrakis(triphenylphosphine) palladium (0) (20 mg) in dioxane (1

ml) is subjected to microwave irradiation (200W, 105 °C) in a sealed vessel. After evaporation, the material is purified by passage through an SCX cartridge followed by preparative LC-MS to yield 3-{[2-chloro-4-(6-chloropyridin-3-yl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane (27 mg)

Reaction Scheme 8

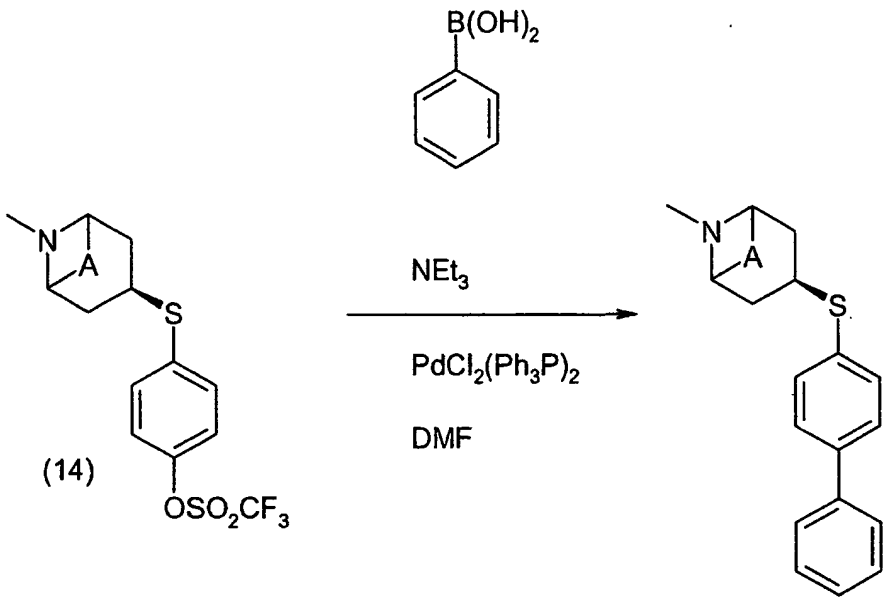
Representative example of an "in situ" Stille coupling:



To a mixture of the triflate (14), 5-bromopyrimidine, lithium chloride and tetrakis(triphenylphosphine) palladium (0) under nitrogen is added hexamethylditin and dioxane. The mixture is heated under reflux and then poured into a mixture of aqueous potassium fluoride and ethyl acetate. This mixture is stirred vigorously, passed through a sintered funnel and the layers separated. The organic phase is worked up and purified to yield a Group D compound wherein R^2 is pyrimidinyl.

Reaction Scheme 9

Representative example of a Suzuki coupling:

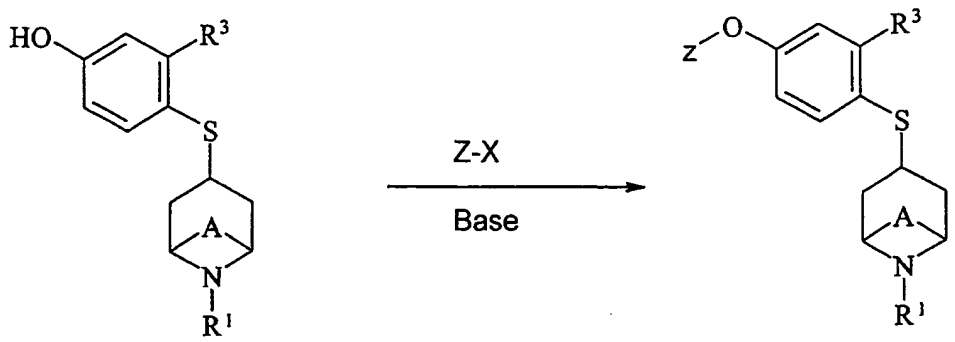


To a mixture of the triflate (14) and phenylboronic acid in DMF is added followed by dichlorobis(triphenylphosphine) palladium (II). The solution is heated at about 90 °C for about 4 hours, cooled to room temperature and diluted with ethyl acetate. The reaction mixture is worked up and purified to a Group D compound wherein R^2 is phenyl.

Compounds of Group E (R^2 is $(L)_a$-Z) may be prepared by a procedure exemplified in Reaction Schemes 10 to 13.

While Reaction Schemes 10 to 13 exemplify compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Reaction Scheme 10



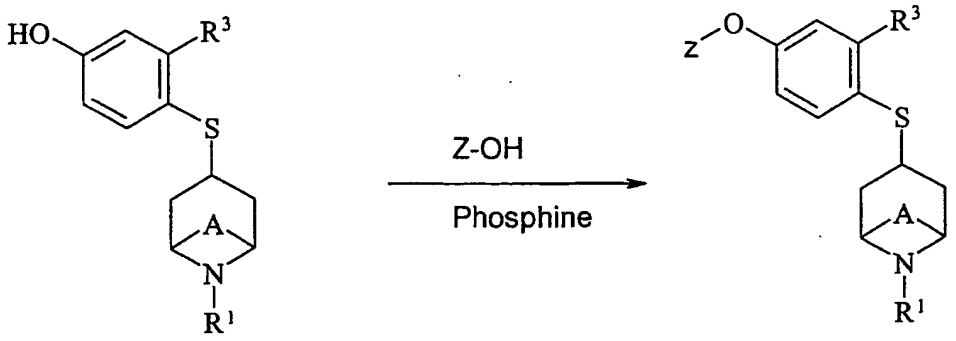
(4) (15)

Phenol (4) is coupled with a compound of formula Z-X wherein X is a suitable leaving group such halogen, trifluoromethanesulfonyl, tosyl or mesyl and Z is C_{1-3}alkyl-F, C_{0-3}alkyl-aryl-R^6, C_{1-3}alkyl-CN, C_{0-3}alkyl-CO-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{0-3}alkyl-SO_2-R^6, C_{0-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6 or C_{1-3}alkyl-NR^6_2, wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl.

The coupling reaction is preferably performed in a dipolar solvent such as ethanol, THF, DMSO, acetonitrile or DMF. More preferably the reaction is performed in DMF or DMSO. The coupling reaction is preferably promoted by a suitable base such as potassium hydroxide, sodium hydride, sodium ethoxide, cesium carbonate, potassium carbonate, potassium fluoride, BEMP, polystyrene-supported BEMP or DBU. More preferably, the coupling reaction is performed in the presence of cesium carbonate, potassium fluoride, sodium hydride or polystyrene-supported BEMP. Typically the coupling reaction may be carried out over a temperature range of from –78 to 150°C. Preferably, the reaction is carried out at a temperature in the range of from room temperature to 70°C. Reaction times for the coupling reaction are typically from 10 minutes to 24 hours. Preferred reaction times are in the range of 30 minutes to 12 hours. In some cases microwaves were applied.

Alternatively, some of the above compounds may be used as key intermediates for other compounds of the subgroup E with methods known by those skilled in the art.

Reaction Scheme 11

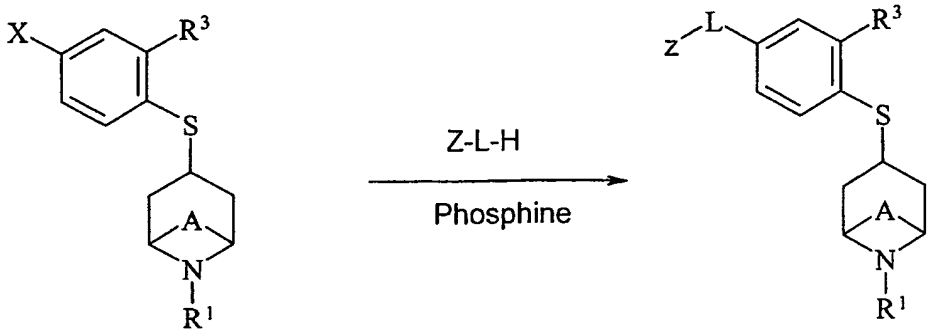


(4) (16)

Phenol (4) is coupled with a compound of formula Z-OH wherein Z is C_{1-3}alkyl-F, C_{1-3}alkyl-aryl-R^6 wherein the C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl.

A mixture solution of the phenol (4) was treated with the corresponding alcohol derivative, a phosphine derivative and a diazacarboxylate derivative under microwaves conditions in a polar solvent such as DMF at 150 °C over 1-4 hours. The reaction mixtures were passed through SCX cartridge eluting with methanol and then 2M ammonia in methanol and concentrated to dryness. The materials were then further purified by preparative LC-MS.

Reaction Scheme 12

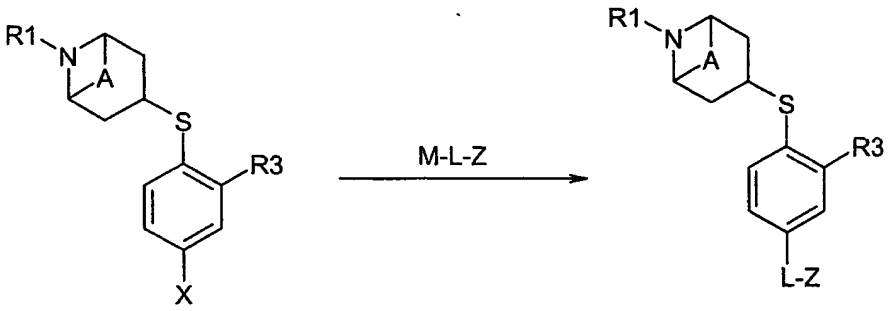


(17)

Phenol derivative, wherein X is trifluoromethanesulfonyl, iodo, chloro or bromo, is coupled with a compound of formula Z-L-H wherein L is NH or $N(C_{1-4}alkyl)$, Z is $C_{1-3}alkyl$-F, $C_{0-3}alkyl$-aryl-R^6, $C_{0-3}alkyl$-CN, $C_{0-3}alkyl$-CO-R^6, $C_{0-3}alkyl$-CO-NR^6_2, $C_{0-3}alkyl$-CO_2-R^6, $C_{0-3}alkyl$-SO_2-R^6, $C_{0-3}alkyl$-SO_2-NR^6_2, $C_{1-3}alkyl$-OR^6 or $C_{1-3}alkyl$-NR^6_2 wherein each $C_{0-3}alkyl$ or $C_{1-3}alkyl$ portion is optionally substituted with from 1 to 6 groups selected from F and $C_{1-5}alkyl$.

A derivative of Pd (0), a phosphine ligand and a suitable base such $CsCO_3$ were charged in a schlenk flask evacuated and filled with argon. Then the corresponding aryl derivative, more preferably (13), with the desired amine were added under argon. The reaction was carry out in an organic solvent such as THF or toluene and the mixture was heating at 100°C overnight. The reaction was concentrated in vacuo and purified in SiO_2 to obtain the final compounds.

Reaction Scheme 13



The intermediate thiobenzene, more preferably triflate (14), is coupled with compounds M-L-Z by displacement of M using palladium (II) salts as a catalyst and in the presence of phosphines. Suitable palladium (II) salts will be readily apparent to the person skilled in the art. The coupling reaction is performed in an organic solvent such as methanol, dioxane, acetonitrile, THF or DMF. Typically the coupling reaction may be carried out over a temperature range of from 0 to 150°C. Preferably, the reaction is carried out at a temperature in the range of from room temperature to 100°C. Reaction times for the coupling reaction are from 3 hours to 48 hours.

In this scheme, M is H or metal, X is Cl, Br, I, or trifluoromethanesulfonyl, L is C_1alkyl and Z is $C_{1-3}alkyl$-F, $C_{1-3}alkyl$-aryl-R^6, $C_{1-3}alkyl$-CN, $C_{1-3}alkyl$-CO-R^6, $C_{1-3}alkyl$-CO-

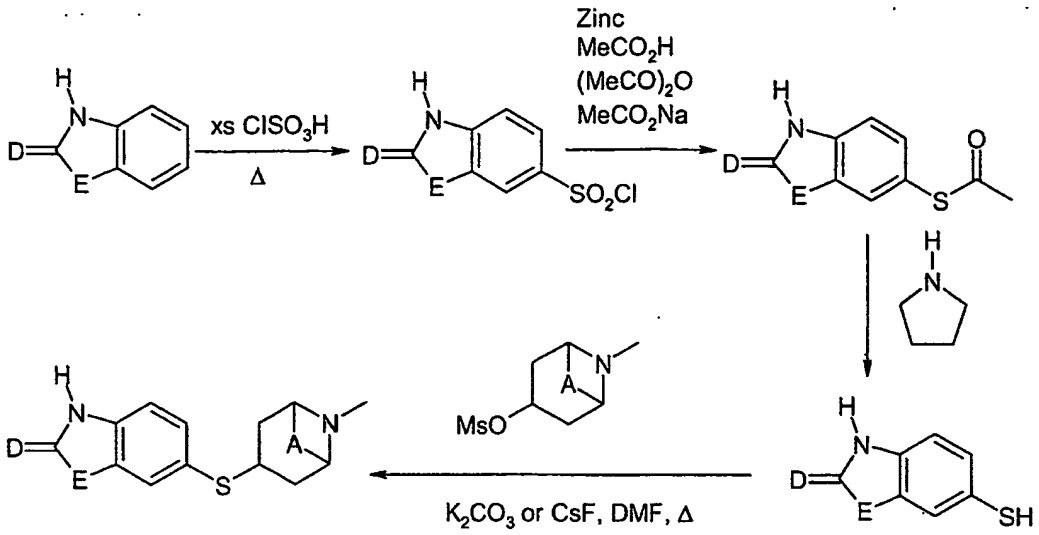
NR^6_2, C_{1-3}alkyl-CO_2-R^6, C_{1-3}alkyl-SO_2-R^6, C_{1-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6 or C_{1-3}alkyl-NR^6_2 wherein the C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl.

The intermediate thiobenzene, more preferably triflate (14), is coupled with compounds M-L-Z by displacement of M using palladium (II) salts as a catalyst and in the presence of phosphines. Suitable palladium (II) salts will be readily apparent to the person skilled in the art. The coupling reaction is performed in an organic solvent such as methanol, dioxane, acetonitrile, THF or DMF. Typically the coupling reaction may be carried out over a temperature range of from 0 to 150°C. Preferably, the reaction is carried out at a temperature in the range of from room temperature to 100°C. Reaction times for the coupling reaction are from 3 hours to 48 hours.

Alternatively, some of the above compounds may be used as key intermediates for other compounds of the subgroup E with methods known by those skilled in the art.

Compounds of Group F^1 and F^2 may be prepared by procedures exemplified in Reaction Schemes 14 to 17. While the Schemes exemplify compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

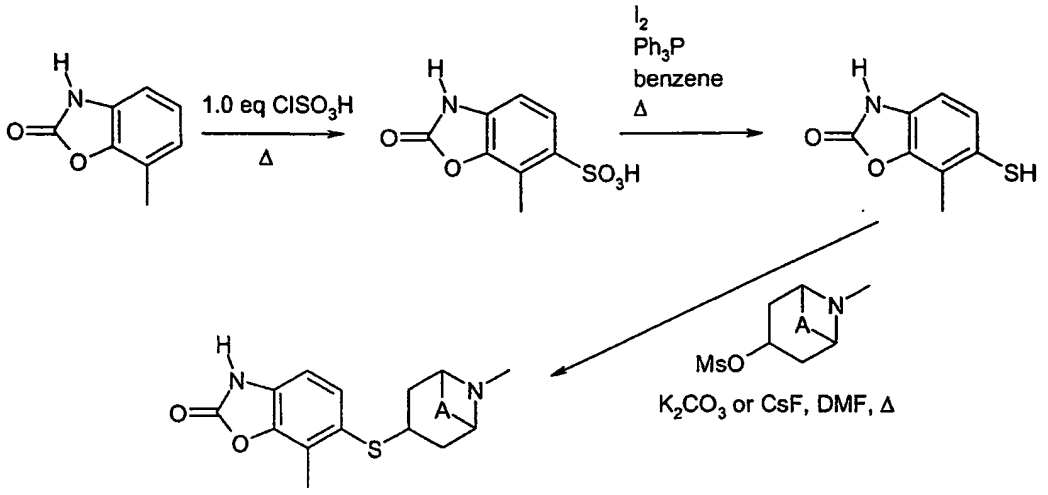
Reaction Scheme 14



Unsubstituted precursors to compounds of group F^1 and F^2 (wherein R^3 = H, R^4 = H, D = O or S and E = O, S, NH, O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-O, CR^5_2-S, CR^5_2-NR^5, CR^5_2-CR^5_2, CO-NR^5, or CR^5=CR^5) may be treated with excess chlorosulphonic acid to selectively introduce a chlorosulphonyl group para to the N-H. The chlorosulphonic acid may be used neat or in a solvent such as chloroform or dichloromethane at a temperature between 0 and 100 °C. Reduction to the acetylthio compound may be effected with zinc, acetic anhydride and acetic acid at a temperature between 0°C and ambient temperature. Removal of the acetyl group may be effected by a secondary amine such as pyrollidine and subsequent alkylation of the free thiol with an appropriate mesylate may be mediated by a base such as potassium carbonate or cesium fluoride in an aprotic solvent such as dimethylformamide. This reaction is performed between ambient temperature and 100°C. It will be appreciated by those skilled in the art that exo and endo isomers may be obtained and these can be separated by crystallisation or chromatography.

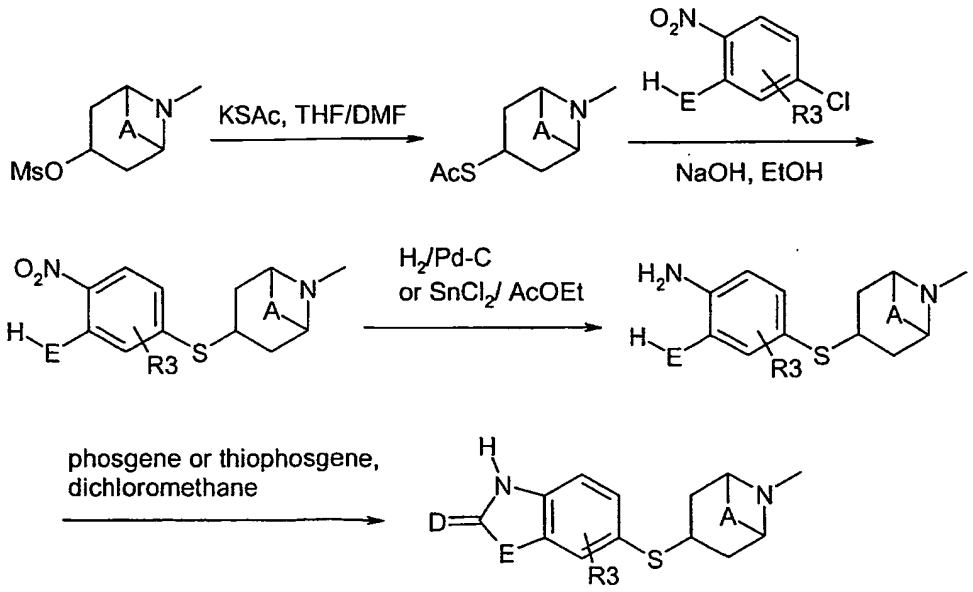
An alternative route to aryl thiols is shown in scheme 15 for D = E = O and R^3 = Me. This utilises 1 equivalent of chlorosulphonic acid at 0 °C and ambient temperature to give a sulphonic acid derivative which may be reduced directly to a thiol using iodine and triphenylphosphine in a solvent such as benzene at reflux under Dean and Stark conditions.

Reaction Scheme 15



Substituted compounds of group F^1 and F^2 (R^3 = H, Cl, R^4 = H, D = O, S and E = O, S, NR^5, O-CR^5_2, NR^5-CR^5_2, NR^5-CO) may be prepared by a route exemplified in Scheme 16.

Reaction Scheme 16

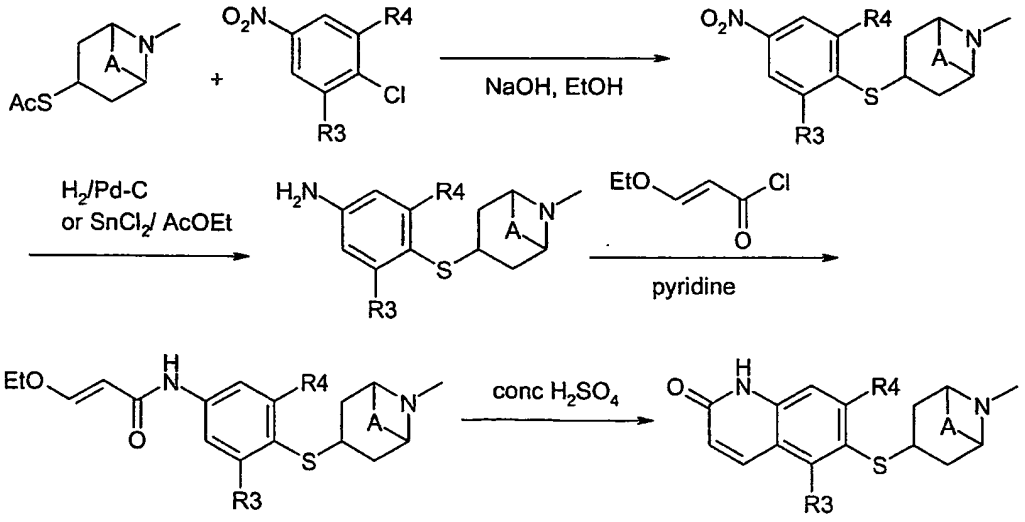


Reaction of a mesylate with potassium thioacetate in an aprotic solvent such as a mixture of dimethylformamide and tetrahydrofuran at temperatures between ambient and 80 °C

gives rise to an acetylthio derivative. It will be appreciated by those skilled in the art that exo and endo isomers may be obtained and these can be separated by chromatography. These compounds may be used to displace a halo atom (eg chlorine) from an appropriately substituted nitrophenyl derivative in a reaction mediated by a nucleophilic base such as hydroxide at ambient temperature. The resultant nitro derivative may be reduced by catalytic hydrogenation in a protic solvent such as ethanol or by tin chloride in ethyl acetate at reflux temperature. Finally reaction with phosgene (or a synthetic equivalent eg triphosgene) or thiophosgene in a solvent such a s dichloromethane or chloroform at a temperature between ambient and reflux temperature gives rise to the compounds of group F^1 and F^2 specified.

Compounds of Group F^2 where D = O, E = CR^5=CR^5 and R3 = R4 may be prepared by a procedure exemplified in Reaction Scheme 17.

Reaction Scheme 17



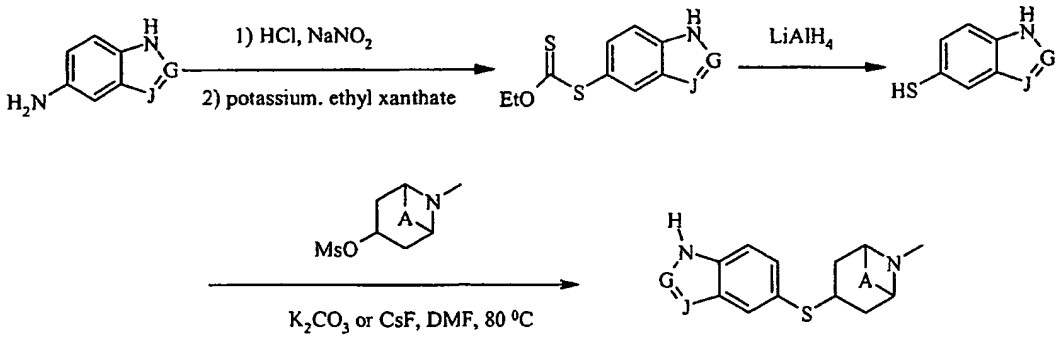
An acetylthio compound may be used to displace a halo atom (eg chlorine) from an appropriately substituted nitrophenyl derivative in a reaction mediated by a nucleophilic base such as hydroxide at ambient temperature. The resultant nitro derivative may be reduced by catalytic hydrogenation in a protic solvent such as ethanol or by tin chloride in ethyl acetate at reflux temperature. The aniline derivative so obtained is acylated with (E)-3-ethoxy-2-propenoyl chloride in a solvent such as dichloromethane in the presence of

a non-nucleophilic base such as pyridine at a temperature between 0 °C and ambient temperature. The resultant amide may be cyclized with a concentrated mineral acid such sulphuric acid at a temperature between 0 °C and ambient temperature.

Compounds of Group G may be prepared by procedures exemplified in Reaction Schemes 18 to 19. While the Schemes exemplify compounds of the present invention wherein m = n = 1, it will be readily apparent to the skilled person that the same procedures may be applied to other ring sizes (i.e. when the sum of m, n, o and p is 3 or more).

Compounds of group G where G is CR^5 or N; and J is CR^5 or N may be prepared by the route exemplified in Scheme 18.

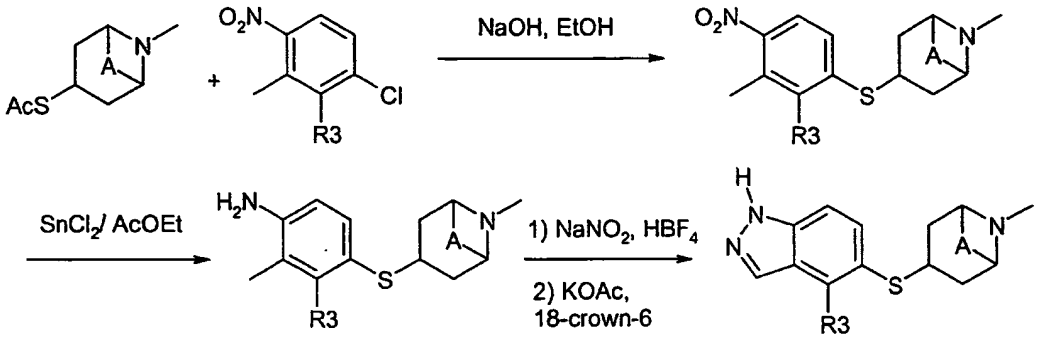
Reaction Scheme 18



An appropriate amino derivative is diazotised under standard conditions (sodium nitrite, hydrochloric acid at or around 0 °C) and treated with potassium ethyl xanthate in water at or around 80 °C. The resulting xanthate may be converted to a thiol using a reducing agent such as lithium aluminium hydride in an aprotic solvent such as diethyl ether or tetrahydrofuran at a temperature between 0 °C and ambient temperature. Subsequent alkylation of the thiol with an appropriate mesylate may be mediated by a base such as potassium carbonate or cesium fluoride in an aprotic solvent such as dimethylformamide. This reaction is performed between ambient temperature and 100°C. It will be appreciated by those skilled in the art that exo and endo isomers may be obtained and these can be separated by crystallisation or chromatography.

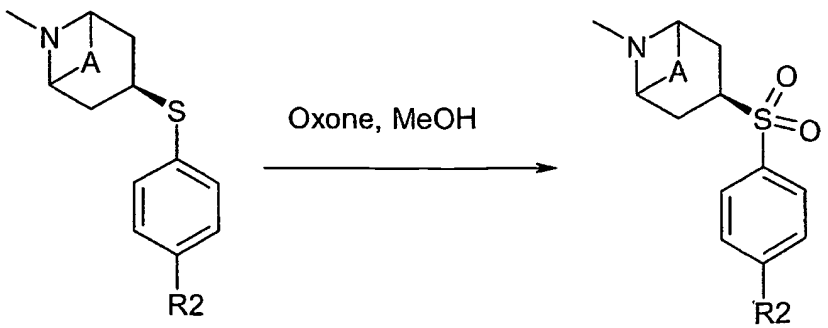
A subgroup of compounds of the type G where J = CR^5, G = N and R3 = Cl may be prepared by a route shown in Scheme 19.

Reaction Scheme 19



An acetylthio compound may be used to displace a halo atom (eg chlorine) from an appropriately substituted ortho-nitrotoluene derivative in a reaction mediated by a nucleophilic base such as hydroxide at ambient temperature. The resultant nitro derivative may be reduced by tin chloride in ethyl acetate at reflux temperature. This is followed by reaction with sodium nitrate in aqueous fluorboric acid at a temperature between 0 °C and ambient temperature. Treatment of the subsequent diazonium tetrafluoroborate salt with potassium acetate and 18-crown-6 in a solvent such as chlororform at ambient temperature gives the appropriate indazole derivatives.

The oxidation of sulfides to sulfones may be achieved by reaction with oxone as shown in Reaction Scheme 20.

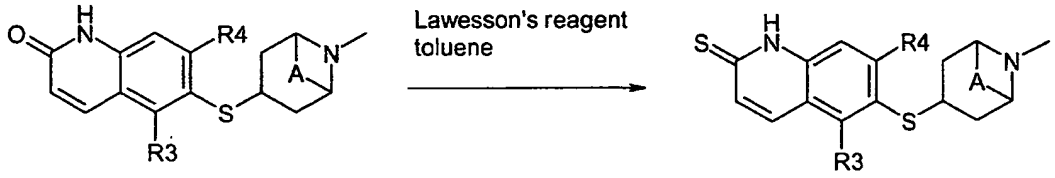


Reaction Scheme 20

To a solution of the azabicylothiophenyl in methanol is added a solution of Oxone in water. The mixture is stirred at room temperature for about 30 minutes and then purified to yield the azabicylosulfonylphenyl.

The conversion of C=O moieties to C=S may be achieved by reaction with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide)] in a solvent such as toluene at refluxing temperature as shown in Scheme 21.

Reaction Scheme 21



The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and

salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, arginine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride. iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

Another aspect of the present invention is a pharmaceutical composition comprising a compound of formula (I) substantially as described hereinbefore with a pharmaceutically acceptable diluent or carrier.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate and lactose. Corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatine. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Compounds of the invention have been demonstrated to be active at the neuronal nicotinic, beta 4 receptor. Their functional agonist activity has been demonstrated in the test described below.

Functional Ca-flux Assay

HEK 293 cell lines expressing different nicotinic receptor β4 subtypes are plated at a density of 50,000 cells/well into poly-D-lysine coated 96 well microtitre plates. Twenty-four hours later the cells are washed with buffer and loaded with Fluo-3 dye (10 M) at room temperature for 1h. The dye is removed and 180 µl of buffer containing atropine at 3µM added.

The plates are loaded into a FLIPR (Molecular Devices) and 20µl of experimental compound are added in a concentration gradient across the plate. The stimulation of the nicotinic receptor response to compound addition is measured as a rise in fluorescence which correlates to the entry of calcium into the cell. Acetylcholine is added 10 min later to all wells to investigate whether the compounds can block the acetylcholine stimulated nicotine response.

The effects of compounds as nicotinic agonists and antagonists are calculated using an OMM (Oxford matrix management) curve fit package.

The present invention further provides compounds of formula (I) or compositions as hereinabove described for use in therapy.

The present invention further provides the use of a compound as hereinbefore described for the manufacture of a medicament for the treatment of a condition indicating treatment with a beta 4 subtype selective nicotinic acetylcholine receptor modulator.

The present invention further provides a method of treatment of a condition indicating treatment with a beta 4 subtype selective nicotinic acetylcholine receptor modulator comprising administering an effective amount of a compound or a composition as hereinbefore described to a patient in need thereof.

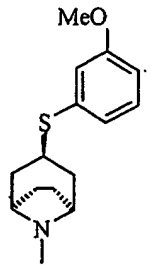
The present invention further provides the use of compounds of formula (I) in the manufacture of a medicament for the treatment of dysfunctions of the central and autonomic nervous systems. Such dysfunctions included, for example, dementia, cognitive disorders, neurodegenerative disorders, extrapyramidal disorders, convulsive disorders, cardiovascular disorders, endocrine disorders, eating disorders, affective disorders, and drug abuse.

The present invention further provides a method of treatment of dysfunctions of the central and autonomic nervous systems comprising administering an effective amount of a compound of formula (I) or a composition as hereinabove described to a patient in need thereof.

The present invention is now further illustrated by means of the following Examples.

Example 1

a) Exo-3-(3-methoxyphenylthio)-8-methyl-8-azabicyclo[3.2.1]octane



NaH (60% dispersion in mineral oil, 101mg, 2.55mmol) was washed with petroleum ether 40-60 (2 x 20ml) under a flow of nitrogen, then treated with THF (~40ml) generating a grey cloudy mixture. This mixture was treated with 3-methoxybenzenethiol (0.30ml, 2.32mmol), causing the evolution of gas and the reaction to become clear. After ten minutes the reaction was treated with 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (500mg, 2.32mmol) as a solution in THF (3 x 15ml). The reaction was stirred at reflux under a flow of nitrogen overnight then concentrated *in vacuo* to a white sticky solid. This solid was dissolved in a mixture of H_2O (40ml) and $CHCl_3$ (40ml) then acidified using 2N $HCl_{(aq)}$ to pH = 2. The organic layer was removed and the aqueous washed with more $CHCl_3$ (2 x 40ml). The aqueous layer was basified using 2N NaOH (pH ~ 10) then extracted using $CHCl_3$ (45ml) and ethyl acetate (40ml). The organic extractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a clear colourless oil (250mg, 41%).

δ_H (300MHz; $CDCl_3$) 1.53-1.60 (2H, m, CH_2), 1.77-1.82 (4H, m, 2 x CH_2), 1.99-2.04 (2H, m, CH_2), 2.27 (3H, s, NCH_3), 3.15-3.17 (2H, m, 2 x $NCHCH_2$), 3.28-3.36 (1H, m, HCS), 3.78 (3H, s, Ar-OCH_3), 6.74-6.77 (1H, m, Ar-H), 6.93-6.98 (2H, m, 2 x Ar-H) and 7.16-7.21 (1H, m, Ar-H); LCMS retention time ~ 2.62 min, m/z (FIAPOSES) 264.1 $[(M+H)^+$, 100%].

By proceeding in a similar manner to Example 1(a) but using the appropriate mercaptobenzene derivative, there were prepared the following compounds:

b) **Exo-3-(4-methoxyphenylthio)-8-methyl-8-azabicyclo[3.2.1]octane**

δ_H (300MHz; $CDCl_3$) 1.50 (2H, m, CH_2), 1.65-1.75 (4H, m, 2 x CH_2), 1.98 (2H, m, CH_2), 2.22 (3H, s, NCH_3), 3.05 (1H, m, HCS), 3.18 (2H, m, 2 x $NCHCH_2$), 3.78 (3H, s, Ar-

OCH_3), 6.78 (2H, m, Ar-**H**); 7.38 (2H, m, Ar-**H**); m/z (FIAPOSES) 264.1 [$(M+H)^+$, 100%].

c) Exo-3-(2-chlorophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane

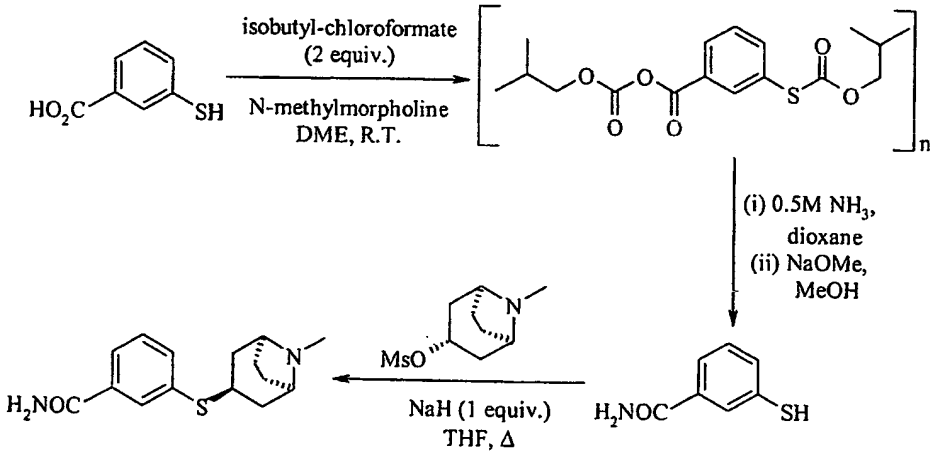
δ_H (300MHz; DMSO) 1.65 (2H, m, CH_2), 1.75-1.85 (4H, m, 2 x CH_2), 1.95 (2H, m, CH_2), 2.30 (3H, s, NCH_3), 3.10 (2H, m, 2 x $NCHCH_2$), 3.60 (1H, m, **H**CS), 7.22 (1H, m, Ar-**H**), 7.40 (1H, m, Ar-**H**), 7.50 (2H, m, Ar-**H**); m/z (FIAPOSES) 268 [$(M+H)^+$, 100%].

d) Exo-3-(phenylthio)-8-methyl-8-azabicyclo[3.2.1]octane

δ_H (300MHz; DMSO) 1.63 (2H, m, CH_2), 1.75-1.85 (4H, m, 2 x CH_2), 2.00 (2H, m, CH_2), 2.30 (3H, s, NCH_3), 3.10 (2H, m, 2 x $NCHCH_2$), 3.30 (1H, m, **H**CS), 7.22 (3H, m, Ar-**H**),), 7.38 (2H, m, Ar-**H**),); m/z (FIAPOSES) 234 [$(M+H)^+$, 100%].

Example 2

Exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide



(i) 3-mercaptobenzamide

To a solution of 3-mercaptobenzoic acid (1.00g, 6.49mmol) in DME (ethyleneglycol–dimethylether, ~15ml) was added *N*-methylmorpholine (1.5ml, 13.6mmol) and *iso*-butylchloroformate (1.77ml, 13.6mmol) under a flow of nitrogen. The clear solution quickly became a cloudy mixture and the temperature started to rise. After stirring for half an hour the reaction was filtered and then treated with 0.5M NH_3 in dioxane (27ml, 13.5mmol). The reaction was treated with sodium methoxide in methanol, then quenched

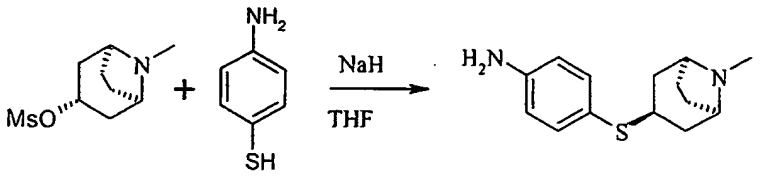
with 2N HCl until pH = 4 and then concentrated *in vacuo* to a white paste. This was partitioned between $CHCl_3$ and H_2O (3 x 100ml) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to a white solid (1.6g). This was dissolved in H_2O, basified (2N NaOH, pH = 10) and the aqueous washed with $CHCl_3$. The aqueous was acidified (2N HCl, pH = 2) then extracted with $CHCl_3$ (2 x 50 ml). The organic extracts were dried ($MgSO_4$) then concentrated *in vacuo* to give 3-mercaptobenzamide as a white solid (501mg).

(ii) Exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide

NaH (60% dispersion in mineral oil, 154mg, 3.84mmol) was washed with petroleum ether 40-60 (3 x 20ml) then treated with THF (60ml) under a flow of nitrogen to give a white cloudy mixture. This mixture treated with 3-mercaptobenzamide (490mg, ~3mmol) as a solution in THF (3 x 10ml), then with 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (490mg, 2.24mmol) as a solution in THF (3 x 5ml) then slowly warmed to reflux. The reaction was maintained at reflux under a flow of nitrogen for two days then concentrated *in vacuo* to a pale yellow solid. This was dissolved in H_2O (50ml), acidified (2N HCl, pH = 2), washed with $CHCl_3$ (50ml) and ethyl acetate (50ml), basified (2N NaOH, pH =10) and extracted with $CHCl_3$ (50ml) and ethyl acetate (50ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a colourless crystalline solid (240mg, 39%), m.p. ~ 147°C; δ_H (300MHz; $CDCl_3$) 1.49-1.61 (2H, m, CH_2), 1.74-1.83 (4H, m, 2 x CH_2), 2.00-2.05 (2H, m, CH_2), 2.27 (3H, s, NCH_3), 3.16-3.18 (2H, m, 2 x $NCHCH_2$), 3.30-3.37 (1H, m, HCS), 5.96-6.24 (2H, m, $CONH_2$), 7.28-7.43 (2H, m, 2 x Ar-H), 7.52-7.55 (1H, m, Ar-H), 7.64-7.66 (1H, m, Ar-H) and 7.84-7.85 (1H, m, Ar-H); LCMS retention time ~ 1.4 min, m/z (FIAPOSES) 277.1 [$(M+H)^+$, 100%].

Example 3

a) **Exo-3-(4-aminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane**



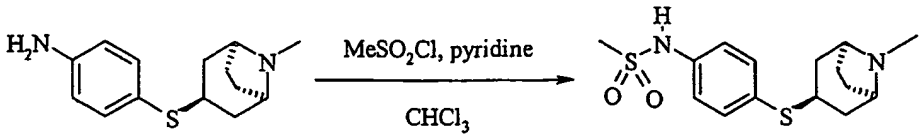
NaH (60% dispersion in mineral oil, 1.59g, 39.8mmol) was washed with petroleum ether 40-60 (2 x 40ml) under a flow of nitrogen, then treated with THF (~120ml) generating a grey cloudy mixture. This mixture was cooled to 0°C then treated with 4-aminothiophenol (4.77g, 38.2mmol) as a solution in THF (4 x 15ml), gas could be seen evolving throughout the addition. After ten minutes the reaction was treated with 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (6.87g, 31.8mmol) as a solution in THF (3 x 20ml) then slowly warmed to reflux. The reaction was refluxed for 5 hours then stirred at room temperature for two days. The reaction was filtered then concentrated *in vacuo* to a brown oil (~ 9g) which was added to acidified water (HCl, pH = 1, 250ml) then washed with $CHCl_3$ (2 x 100ml). The aqueous layer was basified using 2N NaOH (pH ~ 13) then extracted using $CHCl_3$ (3 x 75ml). The organic extractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil (~ 7g). Flash chromatography (SiO_2 100g, gradient elution; $CHCl_3$: MeOH; 100:0 to 90:10) afforded one major fraction. Evaporation gave the title compound as a pale yellow crystalline solid (3.69g, 47%); (m.p. 79-81°C); δ_H (300MHz; $CDCl_3$) 1.48- 1.53 (2H, m, CH_2), 1.63-1.75 (4H, m, 2 x CH_2), 1.94-1.98 (2H, m, CH_2), 2.24 (3H, s, NCH_3), 2.98-3.04 (1H, m, HCS), 3.11-3.13 (2H, m, 2 x $NCHCH_2$), 3.74 (2H, br. s, Ar-NH_2), 6.58-6.61 (2H, m, 2 x Ar-H) and 7.23-7.26 (2H, m, 2 x Ar-H); LCMS retention time ~ 1.57 min, m/z (FIAPOSES) 249.1 [$(M+H)^+$, 60%] and 125.2 (100%).

b) **Exo-3-(3-aminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane**

By proceeding in a similar manner to Example 3(a) but using 3-aminothiophenol, there was prepared the title compound as a yellow solid. δ_H (300MHz; $CDCl_3$) 1.50 (2H, m, CH_2), 1.75-1.85 (4H, m, 2 x CH_2), 2.20 (2H, m, CH_2), 2.25 (3H, s, NCH_3), 3.10 (2H, m, 2 x $NCHCH_2$), 3.25 (1H, m, HCS), 3.60 (2H, br. s, Ar-NH_2), 6.50 (1H, m, Ar-H),), 6.70 (1H, m, Ar-H),), 6.77 (1H, m, Ar-H),), 7.05 (1H, m, Ar-H); m/z (FIAPOSES) 249.1 [$(M+H)^+$, 100%].

Example 4

a) **Exo-3-(4-methanesulphonylaminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane**



To a solution of Exo-3-(4-aminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane (Example 3(a), 250mg, 1.01mmol) in $CHCl_3$ (~75ml) was added pyridine (79mg, 1.01mmol) followed by methanesulphonyl chloride (115mg, 1.01mmol) both as solutions in $CHCl_3$ (2 x 1ml). The pale yellow solution was stirred at room temperature under a flow of nitrogen for two days. Once LCMS showed no more starting material the reaction was quenched with 35% $NH_4OH_{(aq)}$ (~25ml) then extracted with more $CHCl_3$ (25ml). The two organic extracts were combined and washed with $NH_4OH_{(aq)}$ then dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. Excess pyridine which was removed under vacuum, the remaining oil was purified using preparative LCMS, yielding the title compound as a thick sticky paste (117mg, 36%); δ_H (300MHz; $CDCl_3$) 1.88-1.93 (4H, m, 2 x CH_2), 2.22-2.30 (4H, m, 2 x CH_2), 2.60 (3H, s, $^+NCH_3$), 3.00 (3H, s, SO_2CH_3), 3.11-3.18 (1H, m, **H**CS), 3.76 (2H, br. s, 2 x $^+NCHCH_2$), 4.5-5.5 (1H, br. s, Ar-NH), 7.20-7.23 (2H, m, 2 x Ar-**H**), 7.40-7.43 (2H, m, 2 x Ar-**H**) and 8.40 (1H, s, HCO_2^-); LCMS retention time ~ 2.02 min, m/z (FIAPOSES) 327.1 $[(M+H)^+$, 100%].

b) Exo-3-(4-acetylaminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane.

By proceeding in a manner similar to example 4(a) but using acetic anhydride in place of methanesulphonyl chloride there was prepared the title compound as a pale yellow solid. δ_H (300MHz; $CDCl_3$) 1.90-2.00 (4H, m, 2 x CH_2), 2.05-2.20 (4H, m, 2 x CH_2), 2.50 (3H, s, $COCH_3$), 2.60 (3H, s, NCH_3), 3.50 (1H, m, **H**CS), 3.75 (2H, br. s, 2 x $NCHCH_2$), 7.40 (2H, m, 2 x Ar-**H**), 7.65 (2H, m, 2 x Ar-**H**); m/z (FIAPOSES) 291 $[(M+H)^+$, 100%].

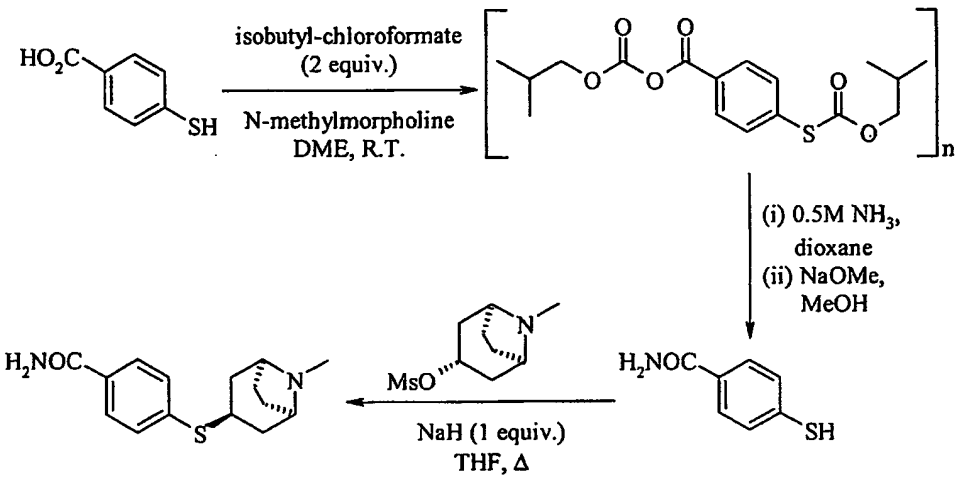
c) Exo-3-(3-acetylaminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane

By proceeding in a manner similar to example 4(a) but using acetic anhydride in place of methanesulphonyl chloride and exo-3-(3-aminophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane [Example 3(b)] there was prepared the title compound as a pale yellow solid. δ_H (300MHz; $CDCl_3$) 1.90-2.10 (4H, m, 2 x CH_2), 2.15-2.20 (4H, m, 2 x CH_2), 2.60 (3H, s, $COCH_3$), 2.65 (3H, s, NCH_3), 3.38 (2H, br. s, 2 x $NCHCH_2$), 3.60

(1H, m, HCS), 7.10 (1H, m, Ar-H),), 7.23 (1H, m, Ar-H),), 7.42 (1H, m, Ar-H),), 7.81 (1H, m, Ar-H); m/z (FIAPOSES) 291 [$(M+H)^+$, 100%].

Example 5

Exo-4-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide



(i) 4-mercaptobenzamide

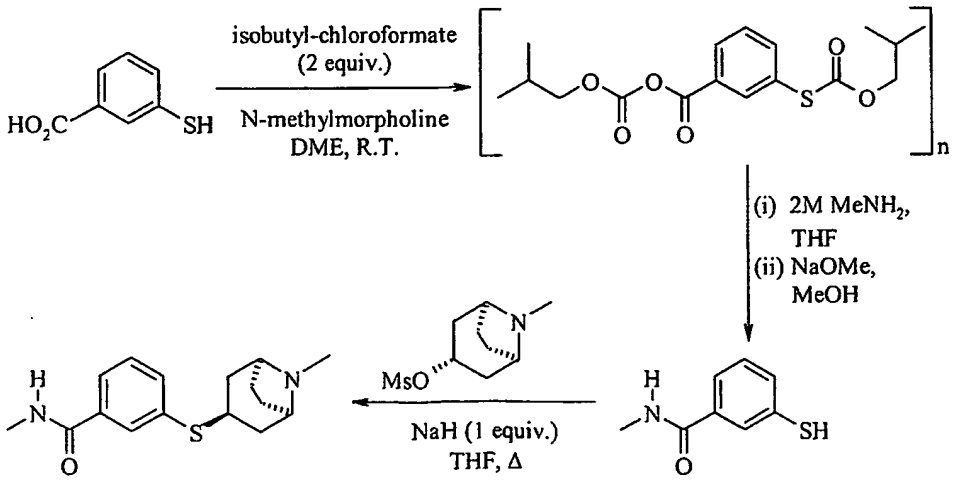
To a stirred solution of 4-mercaptobenzoic acid (1.00g, 6.49mmol) and *N*-methylmorpholine (0.78ml, 7.14mmol) in ethyleneglycol–dimethylether (20ml) was added *iso*-butylchloroformate (0.92ml, 7.14mmol). The reaction was stirred at ambient temperature overnight and filtered to a clear pale yellow solution which was treated with excess ammonia as a solution in dioxane (0.5M, ~15ml). This solution was stirred for two hours at room temperature, and concentrated *in vacuo* to a white solid. The solid was dissolved in a mixture of H_2O (10ml) and $CHCl_3$ (30ml), the aqueous was basified using 2N $NaOH_{(aq)}$ and the organic layer separated and dried ($MgSO_4$) before being concentrated *in vacuo* to a white solid (679mg). The solid was treated with a solution of sodium methoxide in methanol (10ml) and when TLC showed no more starting material, the reaction was acidified using 2N $HCl_{(aq)}$ to pH = 4, then concentrated *in vacuo*. The residue was treated with water and extracted with $CHCl_3$, then concentrated *in vacuo* to give the title compound as an off white solid (376mg).

(ii) Exo-4-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide

NaH (60% dispersion in mineral oil, 96mg, 2.40mmol) was washed with petroleum ether 40-60 (3 x 20ml) under a flow of nitrogen, then treated with THF (~40ml) generating a grey cloudy mixture. This mixture treated with a solution of 4-mercaptobenzamide (~376mg, ~2mmol) in THF (3 x 10ml) then 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (432mg, 2.0mmol) as a solution in THF (3 x 5ml). The reaction was stirred at reflux under a flow of nitrogen overnight then concentrated *in vacuo* to a fine yellow solid. The solid was treated with a mixture of H_2O (20ml) and $CHCl_3$ (20ml) then acidified using 2N $HCl_{(aq)}$ to pH = 2. The organic layer was removed and the aqueous washed with ethyl acetate (20ml). The aqueous layer was basified using 2N NaOH (pH ~ 10) then extracted using $CHCl_3$ (20ml) and ethyl acetate (20ml). The combined organic extractions were dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil (392mg). The oil was purified by preparative LCMS, yielding the title compound as a colourless oil (148mg); δ_H (300MHz; $CDCl_3$) 1.85-1.97 (4H, m, 2 x CH_2), 2.15-2.59 (4H, m, 2 x CH_2), 2.59 (3H, s, $^+NCH_3$), 3.33-3.45 (1H, m, HCS), 3.66 (2H, br. s, 2 x $^+NCHCH_2$), 7.43-7.46 (2H, m, 2 x Ar-H), 7.74-7.76 (2H, m, 2 x Ar-H) and 8.39 (1H, s, HCO_2^-); LCMS retention time ~ 1.55 min, m/z (FIAPOSES) 277.1 [$(M+H)^+$, 100%].

Example 6

Exo- N-methyl 4-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide



(i) N-Methyl 3-mercaptobenzamide

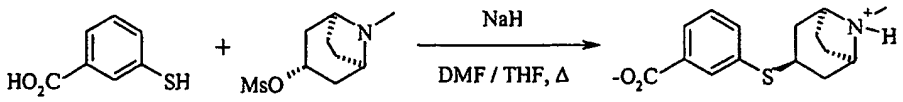
To a solution of 3-mercaptobenzoic acid (1.00g, 6.49mmol) in ethyleneglycol–dimethylether (10ml) was added *N*-methylmorpholine (1.5ml, 13.6mmol) and *iso*-butylchloroformate (1.77ml, 13.6mmol) under a flow of nitrogen at 0°C. The clear solution quickly became a thick paste. After stirring for one hour the reaction was filtered and then treated with 2M methylamine in THF (7ml, 14mmol). The reaction was stirred for two days at room temperature and then treated with 0.5M sodium methoxide in methanol (14ml). The reaction was stirred for three hours, then quenched with 2N HCl until pH = 4 and concentrated *in vacuo* to a semi solid. This was dissolved in H_2O (50ml), basified (2N NaOH, pH = 10), washed with $CHCl_3$ (2 x 50ml), acidified (2N HCl, pH = 2) then extracted with $CHCl_3$ (50 ml) and ethyl acetate (50ml). The organic extracts were combined, dried ($MgSO_4$) then concentrated *in vacuo* to a colourless oil (570mg).

(ii) Exo- N-methyl 4-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzamide

NaH (60% dispersion in mineral oil, 179mg, 4.48mmol) was washed with petroleum ether 40-60 (2 x 20ml) then treated with THF (40ml) under a flow of nitrogen to give a white cloudy mixture. This mixture treated with N-methyl 3-mercaptobenzamide(570mg, ~3.7mmol) as a solution in THF (2 x 10ml), then with 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (572mg, 2.61mmol) as a solution in THF (3 x 5ml). The reaction was heated at reflux under a flow of nitrogen overnight then concentrated *in vacuo* to a pale yellow solid. This was dissolved in H_2O (50ml), acidified (2N HCl, pH = 2) and washed with $CHCl_3$ (50ml) and ethyl acetate (50ml). The aqueous was basified (2N NaOH, pH =10) and extracted with $CHCl_3$ (50ml) and ethyl acetate (50ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil (402mg). Purification by preparative LCMS yielded the title compound as a colourless crystalline solid (300mg, 40%); m.p. ~ 87-89°C; δ_H (300MHz; $CDCl_3$) 1.82-1.99 (4H, m, 2 x CH_2), 2.17-2.36 (4H, m, 2 x CH_2), 2.60 (3H, s, $^+NCH_3$), 2.99-3.01 (3H, d, J = 4.5Hz, $CONCH_3$), 3.20-3.32 (1H, m, HCS), 3.68 (2H, br. s, 2 x $NCHCH_2$), 7.33-7.38 (1H, m, Ar-H), 7.49-7.52 (1H, m, Ar-H), 7.70-7.73 (1H, m, Ar-H), 7.79-7.80 (1H, m, Ar-H) and 8.70 (1H, s, HCO_2^-); LCMS retention time ~ 2.0 min, m/z (FIAPOSES) 291.1 [$(M+H)^+$, 100%].

Example 7

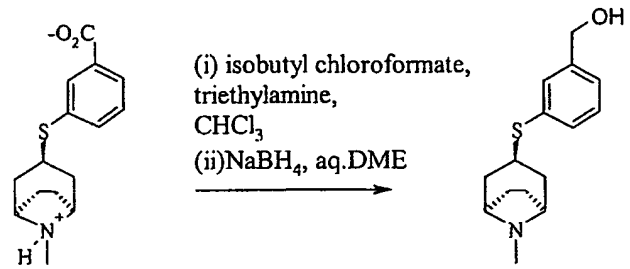
Exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzoic acid



NaH (60% dispersion in mineral oil, 2.18g, 54.5mmol) treated with THF (~210ml) and DMF (70ml), under a flow of nitrogen to give a white cloudy mixture. This mixture treated with 3-mercapto-benzoic acid (4.00g, 25.9mmol) as a solution in THF (6 x 5ml) dropwise over 20 minutes, gas could be seen evolving throughout the addition. Large amounts of a sticky solid began to form in the solution so more DMF (70ml) was added to help solvation. After 30 minutes the reaction was treated with 8-methyl-8-azabicyclo[3.2.1]oct-3-yl methanesulphonate (5.6g, 25.9mmol) as a solution in THF (2 x 10ml) then slowly warmed to reflux for 4 hours. The reaction was stirred at room temperature overnight to give a yellow cloudy mixture which was concentrated *in vacuo* to a thick yellow oil, which could be purified by recrystallising from 10:1 H_2O:CH_3CN to yield the title compound as a crystalline solid (1.65g, 23%); (m.p. 249-251°C); δ_H (300MHz; D_2O) 1.81-2.21 (8H, m, 4 x CH_2), 2.64 (3H, s, $^+NCH_3$), 3.41-3.54 (1H, m, HCS), 3.80 (2H br. s, 2 x $^+NCHCH_2$), 7.32-7.41 (1H, m, Ar-H), 7.47-7.54 (1H, m, Ar-H), 7.74-7.76 (1H, m, Ar-H) and 7.87 (1H, br. s, Ar-H); δ_H (300MHz; methanol d4) 2.01-2.18 (6H, m, 3 x CH_2), 2.29-2.32 (2H, m, CH_2), 2.75 (3H, s, $^+NCH_3$), 3.57-3.60 (1H, m, HCS), 3.88 (2H br. s, 2 x $^+NCHCH_2$), 7.35-7.54 (1H, m, Ar-H), 7.55-7.57 (1H, m, Ar-H), 7.86-7.89 (1H, m, Ar-H) and 8.04-8.05 (1H, m, Ar-H); LCMS retention time ~ 1.9 min, m/z (FIAPOSES) 278.1 [$(M+H)^+$, 100%].

Example 8

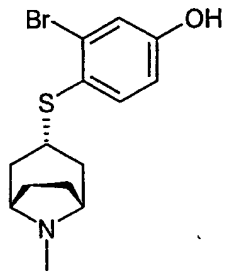
Exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzyl alcohol



A solution of exo-3-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylthio)-benzoic acid (Example 7, 230mg) in chloroform (50ml) was treated with triethylamine (90mg) and isobutyl chloroformate (119mg). After stirring at ambient temperature for 2 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in ethylene glycol dimethyl ether (40ml) and treated dropwise with a solution of sodium borohydride (34mg) in water (2ml) over 30 minutes. After stirring a further 1 hour at ambient temperature, the reaction mixture was partitioned between ethyl acetate (30ml) and water (10ml). The organic layer was dried over magnesium sulphate and and concentrated to dryness. The residue was purified by preparative HPLC to give the title compound (60mg) as a white solid.

Example 9

3-Bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol



(i) 3-Bromo-4-thiocyanato-phenol.

To an ice-cooled suspension of $Pb(SCN)_2$ (1.81g, 5.6mmol) in dry methylene chloride (27mL) $PhICl_2$ (0.97g, 3.54mmol, (prepared according to D. Koyuncu et al., *J. Chem. Res. (S)* **1990**, 21) was added and the resulting mixture was stirred for 30min at 0°C under nitrogen. A solution of 3-bromophenol (250mg, 1.44mmol) in dry methylene chloride (3mL) was added, the mixture was stirred for 2h at 0°C and filtered in cold through a celite® pad washing extensively with ethyl acetate. After addition of silicagel to the filtrate and evaporation of solvents, the mixture was purified by flash chromatography (30% ethyl acetate/hexanes) to afford 0.32g (47%) of the title compound as a brown solid. m.p. 91-92°C.

(ii) 3-Bromo-4-mercaptophenol.

To a hot (85°C) solution of 3-bromo-4-thiocyanato-phenol (315mg, 1.37mmol) in absolute ethanol (10mL) under nitrogen, sodium sulfide nonahydrate (403mg, 2.05mmol) was added. The resulting mixture was stirred at 85°C for 20min. More sodium sulfide nonahydrate (230mg) was added and heating was continued for 15min. The mixture was cooled down, made acidic with 5N acetic acid (10mL) and extracted with methylene chloride (x1). The organic layer was washed once with water, dried and concentrated in vacuo to give the title compound as a yellow solid (259mg, 92%) which was quickly submitted to the next reaction without further treatment.

EIMS M-1: 203.

(iii) 3-Bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol.

To a solution of 3-bromo-4-mercaptophenol (259mg, 1.3mmol) and methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (240mg, 1.1mmol) in dry dimethylformamide (10mL) under nitrogen, potassium carbonate (407mg, 2.75mmol) was added. The resulting mixture was vigorously stirred at room temperature for 18h under nitrogen and 10% hydrochloric acid was added. The mixture was washed with ethyl acetate (x3), the aqueous layer made basic (pH = 8) with solid sodium bicarbonate and extracted with ethyl acetate (x4). The combined organic phase was concentrated in vacuo and purified by flash chromatography (10% Methanol/1% ammonia/methylene chloride) to give the title compound, 170mg (47%).

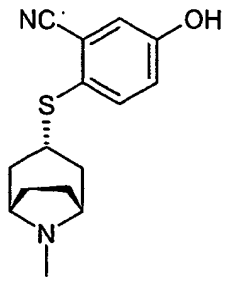
EIMS M+1: 328.

^{1}H NMR (200 MHz, CD_3OD) δ 7.37 (d, *J*= 8.6 Hz, 1 H), 7.07 (d, *J*= 2.7 Hz, 1 H), 6.69 (dd, *J*= 8.4, 2.7 Hz, 1 H), 3.19 (br m, 3 H), 2.25 (s, 3H), 2.05 (m, 2 H), 1.77-1.71 (m, 4 H), 1.60 (d, *J*= 8.0 Hz, 2H).

^{13}C NMR (300 MHz, CD_3OD) δ 160.9, 139.0, 131.9, 124.4, 122.0, 116.9, 63.3, 40.2, 39.8, 39.2, 27.1.

Example 10

5-Hydroxy-2-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-benzonitrile



3-Bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol (35mg, 0.1mmol), zinc cyanide (23mg, 0.2mmol) and DPPF (28mg, 0.05mmol) were dissolved in degassed and dry DMF (0.2mL). To the above mixture, $Pd_2(dba)_3$ (18mg, 0.02mmol) was added and the resulting mixture was stirred at 120°C for 6h, cooled down, diluted with ethyl acetate and filtered through a celite® pad. The filtrate was washed once with a saturated sodium bicarbonate solution and extracted with 10% hydrochloric acid (x2). The aqueous phase was concentrated in vacuo and purified by SCX to afford 5.5mg (20%) of the title compound.

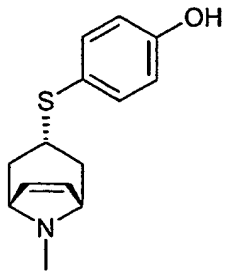
EIMS M+1: 275.

^{1}H NMR (200 MHz, CD_3OD) δ 7.45 (d, *J*= 8.3 Hz, 1 H), 7.05 (d, *J*= 2.7 Hz, 1 H), 6.96 (dd, *J*= 8.6, 2.7 Hz, 1 H), 3.30 (br m, 3 H), 2.30 (s, 3H), 2.08 (m, 2 H), 1.83-1.78 (m, 4 H), 1.67 (d, *J*= 8.3 Hz, 2H).

^{13}C NMR (300 MHz, CD_3OD) δ 160.8, 138.4, 124.0, 121.6, 120.9, 119.7, 117.9, 62.1, 39.5, 38.6, 37.6, 25.6.

Example 11

4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(exo)*-ylsulfanyl)-phenol



(i) Methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(endo)*-yl ester. To a solution of 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ol hydrochloride (from E-Merck, 3.0g, 17.08mmol) in CH_2Cl_2 (30mL) pyridine (2.7mL, 2.64g, 34.16mmol) and

methanesulfonyl chloride (1.6mL, 2.37g, 20.50mmol) were added and the mixture was stirred at 23°C for 72h. Then the reaction was diluted with CH_2Cl_2 and washed successively with aq NH_4OH 32% and brine. The combined aqueous phase was extracted with CH_2Cl_2 and the organic phase was dried and concentrated in vacuo to afford the mesylate as a pale yellow solid (2.2g, 59%) that was used without further purification.

m. p. 64-65°C.

^1H NMR (200 MHz, $CDCl_3$) δ 6.02 (br s, 2 H), 4.88 (t, J = 5.8 Hz, 1 H), 3.39 (br s, 2 H), 2.9 (s, 3 H), 2.36-2.26 (m, 2 H), 2.26 (s, 3 H), 1.98-1.90 (m, 2 H).

(ii) 4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(exo)*-ylsulfanyl)-phenol.

To a mixture of the compound from step A (500mg, 2.3mmol) and 4-mercaptophenol (380mg, 3.0mmol) in dry DMF (15mL), potassium carbonate (920mg, 6.22mmol) was added. The resulting mixture was vigorously stirred at room temperature for 16h. The mixture was diluted with ethyl acetate and extracted with 10% hydrochloric acid (x2). The combined aqueous phase was neutralised with sodium carbonate, extracted with ethyl acetate (x6), dried (Na_2SO_4) and evaporated. The crude was purified by flash chromatography (5% Methanol/1% ammonia/methylene chloride) to give the title compound, 120mg (21%) as a white solid.

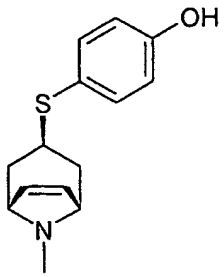
EIMS M+1: 248.

^1H NMR (200 MHz, CD_3OD) δ 7.23 (d, J = 8.6 Hz, 2 H), 6.70 (d, J = 8.6 Hz, 2 H), 5.89 (s, 2 H), 3.47 (br s, 2 H), 2.93 (m, 1 H), 2.15 (s, 3 H), 1.73 (d, J= 3.0 Hz, 2 H), 1.68 (t, J= 2.9 Hz, 2 H).

^{13}C NMR (300 MHz, CD_3OD) δ 159.9, 138.2, 131.0, 124.6, 117.7, 69.1, 41.6, 41.5, 34.5.

Example 12

4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(endo)*-ylsulfanyl)-phenol



To a mixture of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(endo)*-yl ester (326mg, 1.5mmol) and 4-mercaptophenol (210mg, 1.65mmol) in acetone (10mL), K_2CO_3 (1.33g, 9.0mmol) was added. The resulting mixture was stirred at 65°C for 16h. The mixture was diluted with brine and extracted with CH_2Cl_2 (x5), dried (Na_2SO_4) and evaporated. The crude was purified by flash chromatography (8% Methanol/1% ammonia/methylene chloride) to give the title compound, 57mg (15%) as a white solid.

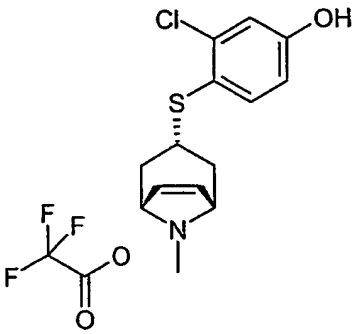
EIMS M+1: 248.

^{1}H NMR (200 MHz, CD_3OD) δ 7.16 (d, J = 8.6 Hz, 2 H), 6.69 (d, J = 8.8 Hz, 2 H), 6.05 (s, 2 H), 3.48 (br s, 2 H), 3.10 (t, J= 7.2 Hz, 1 H), 2.36 (dd, J= 7.3, 3.5 Hz, 1 H), 2.29 (dd, J= 7.4, 3.5 Hz, 1 H), 2.26 (s, 3 H), 1.91 (d, J= 14.2 Hz, 2 H).

^{13}C NMR (300 MHz, CD_3OD) δ 159.3, 136.0, 133.9, 130.1, 117.8, 68.4, 44.1, 42.1, 36.4.

Example 13

3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt



To a mixture of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(endo)*-yl ester (366mg, 1.69mmol) and 3-chloro-4-mercaptophenol (379mg, 2.36mmol) in dry DMF (11mL), K_2CO_3 (675mg, 4.6mmol) was added. The resulting mixture was stirred at room temperature for 16h. The mixture was diluted with ethyl acetate and extracted with 10% hydrochloric acid (x2). The combined aqueous phase was neutralised with sodium carbonate, extracted with ethyl acetate (x6), dried (Na_2SO_4) and evaporated. The crude was purified by flash chromatography (5% Methanol/1% ammonia/methylene chloride) and reverse phase HPLC to give the title compound as a white solid.

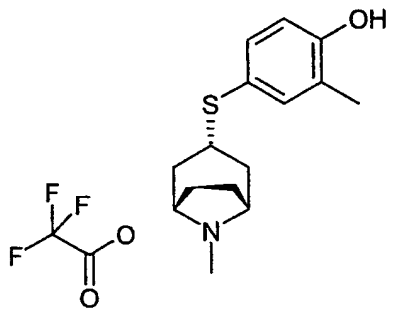
EIMS M+1: 282.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (d, *J*= 8.6 Hz, 1 H), 6.92 (dd, *J*= 2.4 Hz, 1 H), 6.72 (dd, *J*= 8.6, 2.4 Hz, 1 H), 6.13 (d, *J*= 0.8 Hz, 2 H), 4.31 (br s, 2 H), 3.28 (m, 1 H), 2.77 (s, 3 H), 2.17-1.91 (m, 4 H).

^{13}C NMR (300 MHz, $CDCl_3$) δ 160.8, 141.0, 139.6, 128.3, 121.0, 118.2, 116.0, 69.9, 39.2, 38.1, 31.9.

Example 14

2-Methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt



(i) 2-Methyl-4-thiocyanato-phenol.

To an ice-cooled suspension of $Pb(SCN)_2$ (485mg, 1.5mmol) in dry methylene chloride (10mL), $PhICl_2$ (330mg, 1.2mmol) was added and the resulting mixture was stirred for 25min at 0°C under nitrogen. A solution of o-cresol (108mg, 1mmol) in dry methylene chloride (2mL) was added dropwise. The mixture was stirred for 1h at 0°C and filtered through a celite® pad washing extensively with methylene chloride. After addition of silicagel to the filtrate and evaporation of solvents, the mixture was purified by flash chromatography (10% ethyl acetate/hexane) to afford 164 mg (99%) of the title compound as a white solid.

m.p. 64-68°C.

EIMS M+1: 166.

IR (cm^{-1}): 3406, 1637, 1495, 1276, 1180, 814.

^{1}H NMR δ (ppm) (200 MHz, $CDCl_3$): 7.31 (d, *J*= 2.4 Hz, 1 H), 7.23 (dd, *J*= 8.6 Hz, 2.4 Hz, 1 H), 6.79 (d, *J*= 8.6 Hz, 1 H), 2.21 (s, 3 H).

^{13}C NMR δ (ppm) (200 MHz, $CDCl_3$): 155.6 (C), 134.1 (CH), 130.5 (CH), 126.3 (C), 115.7 (CH), 111.9 (C), 111.0 (C), 14.8 (CH_3).

(ii) 2-Methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt.

To a solution of 2-methyl-4-thiocyanato-phenol (160mg, 0.97mmol) in absolute ethanol (8mL) under nitrogen, sodium sulfide nonahydrate (298mg, 1.16mmol) was added. The resulting mixture was stirred at 85°C for 30min and a solution of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (254mg, 1.16mmol) in absolute ethanol (4mL) was added dropwise at 85°C. The mixture was stirred for 2 h. The solvent was removed in vacuo and residue was submitted to a SCX collecting a mixture exo/endo. This mixture was purified by reverse phase HPLC to obtain the title compound (20mg, 5%).

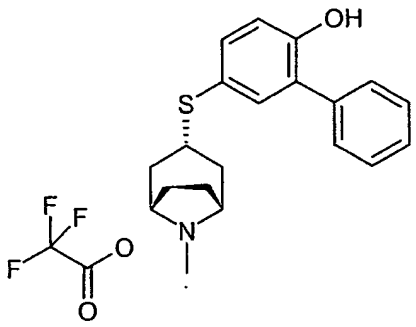
EIMS M+1: 264.

^{1}H NMR δ (ppm) (200 MHz, $CDCl_3$):7.20 (d, *J*= 2 Hz, H-7, 1 H), 7.12 (dd, *J*= 8 Hz, 2 Hz, H-11, 1 H), 6.74 (d, *J*= 8 Hz, H-10, 1 H), 4.87 (br s, ArOH, 1 H), 3.82 (br, H-2, 2 H), 3.02 (m, H-5, 1 H), 2.66 (d, *J*= 4.8 Hz, $\underline{CH_3}$-N^+H, 3 H), 2.23 (m, H-3, 4 H), 2.20 (s, CH_3Ar, 1 H), 1.97 (m, H-4, 2 H), 1.93 (m, H-4, 2 H).

^{13}C NMR δ (ppm) (200 MHz, $CDCl_3$): 156.2 (C, C-9), 138.7 (CH, C-7), 135.0 (CH, C-11), 125.8 (C, C-8), 120.6 (C, C-6), 116.1 (CH, C-10), 63.9(2CH, C-2), 39.2 (CH_3, $\underline{CH_3}$-N^+H, C-1), 36.9 ($2CH_2$, C-4), 36.6 (CH, C-5), 24.9 ($2CH_2$, C-3), 16.3 (CH_3, CH_3Ar).

Example 15

5-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-biphenyl-2-ol, trifluoroacetate salt



(i) 5-Thiocyanato-biphenyl-2-ol.

To an ice-cooled suspension of $Pb(SCN)_2$ (569mg, 1.76mmol) in dry methylene chloride (10mL), $PhICl_2$ (390mg, 1.42mmol) was added and the resulting mixture was stirred for

30min at 0°C under nitrogen. A solution of 2-phenyl-phenol (200mg, 1.18mmol) in dry methylene chloride (5mL) was added dropwise. The mixture was stirred for 18h at room temperature and filtered through a celite® pad washing extensively with methylene chloride. After addition of silica gel to the filtrate and evaporation of solvents, the mixture was purified by flash chromatography (10% ethyl acetate/hexane) to afford 171mg (64%) of the title compound.

EIMS M+1: 228.

IR (cm^{-1}): 3405, 1638, 1446, 1280, 1073.

^1H NMR δ (ppm) (200 MHz, $CDCl_3$): 7.44-7.35 (m, 7 H), 6.98 (d, *J*= 8.6 Hz, 1H).

^{13}C NMR δ (ppm) (200MHz, $CDCl_3$): 155.5 (C), 136.0 (C), 134.9 (CH), 133.4 (CH), 131.1 (C), 129.6 ($2CH_2$), 129.5 ($2CH_2$), 128.9 (CH), 118.5 (CH), 113.8 (C), 112.5 (C).

(ii) 5-Mercapto-biphenyl-2-ol.

To a solution of 5-thiocyanato-biphenyl-2-ol (160mg, 0.97mmol) in absolute ethanol (8mL) under nitrogen, sodium sulfide nonahydrate (298mg, 1.16mmol) was added. The resulting mixture was stirred at 85°C for 20min. The mixture was cooled down, made acidic with 10% aqueous HCl and extracted with ethyl acetate (x2). The combined organic layers were dried on $MgSO_4$ and concentrated in vacuo to give the title compound as a yellow solid (105mg, 95%) which was quickly submitted to the next reaction without further purification.

EIMS M-1: 201.

(iii) 5-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-biphenyl-2-ol, trifluoroacetate salt.

To a solution of 5-mercapto-biphenyl-2-ol (105mg, 0.52mmol) in anhydrous acetone (3ml), potassium carbonate (720mg, 5.2mmol) was added at room temperature. The mixture was stirred under nitrogen atmosphere and methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (103mg, 0.47mmol) in acetone (2ml) was added dropwise. The resulting mixture was vigorously stirred at 70°C for 18h under nitrogen and was filtered and the solvent was removed in vacuo. The resulting residue was purified by reverse phase HPLC to afford the title compound (38mg, 17%).

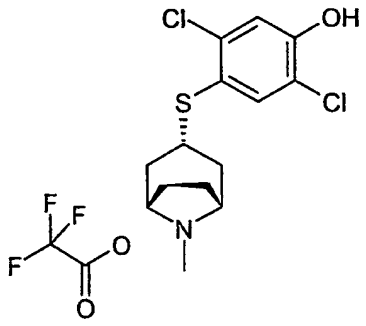
EIMS M+1: 264.

^{1}H NMR δ (ppm) (500 MHz, DMSO): 9.94 (br s, OH, 1 H), 9.31 (br s, NH, 1 H), 7.55 (d, *J*= 7.3 Hz, H-13, 2 H), 7.41 (t, *J*= 7.3 Hz, H-14, 2 H), 7.33 (m, H-7, 1 H), 7.32 (m, H-15, 1 H), 7.28 (dd, *J*= 8.5, 2.6 Hz, H-11, 1 H), 6.96 (d, *J*= 8.5 Hz, H-10, 1 H), 3.82 (br s, H-2, 2 H), 3.35 (m, H-5, 1 H), 2.59 (d, *J*= 5.1 Hz, CH_3-N+H, 3 H), 2.14 (m, H-3, 2 H), 1.97 (m, H-4, 2 H), 1.86 (t, *J*= 12.3 Hz, H-4, 2 H), 1.92 (m, H-3, 2 H).

^{13}C NMR δ (ppm) (125 MHz, DMSO): 154.9 (C, C-9), 137.6 (C, C-12), 136.9 (CH, C-7), 135.2 (CH, C-11), 129.0 (2CH, C-13), 128.4 (C, C-8), 127.9 (2CH, C-14), 126.8 (CH, C-15), 116.7 (CH, C-10), 63.1 (2CH, C-2), 38.0 (CH_3, $\underline{CH_3}$-N$^+$H, C-1), 36.2 ($2CH_2$, C-4),35.3 (CH, C-5), 23.5 ($2CH_2$, C-3).

Example 16

2,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3*(exo)*-ylsulfanyl)-phenol



(i) 2,5-Dichloro-4-hydroxy-benzenesulfonyl chloride.

2,5-Dichlorophenol (1.00g, 6.17mmol) was gradually added to chorosulfonic acid (2mL, 30.85mmol) at 0°C. Then it was heated at 80°C for 1hour. Then it was cooled at room temperature and poured onto crushed ice. Then ethyl acetate was added. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo to give 1.30g (81%) of the title compound as a white solid, which was used in the next reaction without further purification.

EIMS M-1: 259.

(ii) 2,5-Dichloro-4-mercaptophenol.

To a mixture of 2,5-dichloro-4-hydroxy-benzenesulfonyl chloride (1.28g, 4.92mmol) and a solution of 25% of H_2SO_4 (17mL), Zinc dust (1.64g, 24.56mmol) was added slowly at

room temperature. The reaction mixture was allowed to stir at 120°C overnight. The mixture was then cooled at room temperature and toluene was added. The layers were separated and the aqueous phase was dried over, $MgSO_4$ filtered and concentrated in vacuo to give 514mg (54%) of the title compound as a white solid, which was used in the next reaction without further purification.

EIMS: 193.

(iii) 2,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3*(exo)*-ylsulfanyl)-phenol.

To a solution of 2,5-dichloro-4-mercaptophenol (487mg, 2.51mmol) in acetone (5mL), K_2CO_3 (3.20g, 22.8mmol) and a solution of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (500mg, 2.28mmol) in acetone (5 mL) were added at room temperature. The resulting mixture was allowed to stir under reflux overnight. The mixture was concentrated in vacuo. The crude was purified first by Chromatography (Strong Cation Exchange, 2M ammonia in methyl alcohol) and then by reverse phase HPLC to afford the title compound (78mg, 8%) as a white solid.

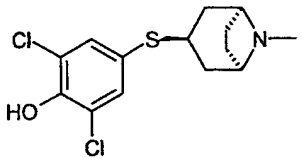
m. p. 193-194°C.

EIMS M+1: 318.

^{1}H NMR δ (ppm) (200 MHz, MeOH-d4): 7.59 (s, 1 H), 7.06 (s, 1 H), 3.88 (s, 2 H), 3.49 (m, 1 H), 2.72 (s, 3 H), 2.31-1.88 (m, 8 H).

Example 17

3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-*(exo)*-ylsulfanyl)-phenol



(i) 3,5-Dichloro-4-hydroxy-benzenesulfonyl chloride.

3,5-Dichlorophenol (2.43 g, 14.9 mmol) was gradually added to chorosulfonic acid (4.9 mL, 74.6 mmol) at 0 °C. Then it was heated at 80 °C for 1hour. Then it was cooled at room temperature and poured onto crushed ice. The resulting white solid was filtered and

washed with cool water. The solid was dissolved in EtOAc and dried over $MgSO_4$, filtered and and concentrated in vacuo (CIV) to give 2.24 g (58%) of the title compound as a white solid, which was used in the next reaction without further purification.
Ion Electrospray Mass Spectrum M-1: 259.

(ii) Acetic acid 2,6-dichloro-4-thiocyanato-phenyl ester.
To compound from step (i) (1.00 g, 3.85 mmol), acetic acid (16 mL), acetic acid (16 mL), acetic anhydride (5.5 mL) and sodium acetate (1.60 g, 19.5 mmol) were added at room temperature. After stirring for 5 min., zinc dust (1.60 g) was added. The mixture was refluxed for 2 hours. Then it was cooled and the resulting solid was filtered, and the solvent was removed under vacuo. The residue was triturated with water, filtered and washed with water. The resulting solid was dissolved with CH_2Cl_2, dried over $MgSO_4$, filtered and CIV, affording 700 mg (65%) of the final compound as a white solid.

(iii) Acetic acid 2,6-dichloro-4-mercaptophenyl ester.
To a suspension of compound from step (ii) (472 mg, 1.69 mmol) in MeOH (17 mL), a solution of sodium thiomethoxide (130 mg, 1.86 mmol) in MeOH (4 mL) was added at room temperature. The reaction mixture was allowed to stir at rt, under nitrogen atmosphere overnight. Then it was concentrated in vacuo and a 0.1 M solution of HCl (30 mL) and CH_2Cl_2 were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered and CIV to afford 315 mg (79%) of the final compound as a white solid.
Ion Electrospray Mass Spectrum M+1: 237.

(iv) 3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-*(exo)*-ylsulfanyl)-phenol.
To a suspension of NaH (35 mg, 1.40 mmol) in dry THF (10 mL), under nitrogen atmosphere, a solution of compound from step (iii) (300 mg, 1.27 mmol) in dry THF (5 mL) was added at room temperature. The mixture was allowed to stir at this temperature for 15 min. Then a solution of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (252 mg, 1.15 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred under reflux for 2 days. Then it was cooled and concentrated in vacuo. The crude was purified first by chromatography (Strong Cation Exchange, 2M ammonia in methyl

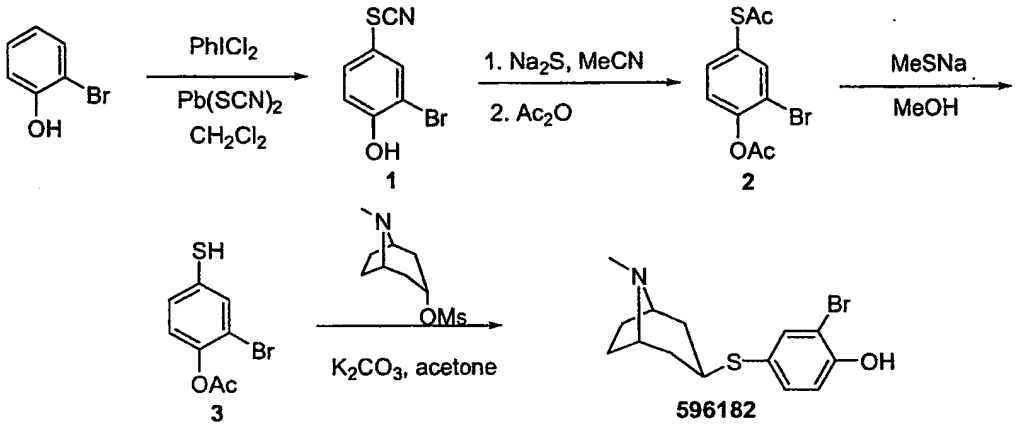
alcohol) giving an exo/endo mixture. This mixture was purified by reverse phase HPLC to obtain the title compound (5.6 mg, 1%) as a white solid.

Ion Electrospray Mass Spectrum M+1: 318

^{1}H NMR δ (ppm) (200 MHz, MeOH-d4): 7.45 (s, 2 H), 3.87 (br s, 2 H), 3.49-3.38 (m, 1 H), 2.72 (s, 3 H), 2.31-1.83 (m, 8 H).

Example 18

2-Bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-*(exo)*-ylsulfanyl)-phenol



(i) 2-bromo-4-thiocyanatophenol

To a suspension of lead thiocyanate (6.49 g, 20.05 mmol) in CH_2Cl_2 (125 mL) under nitrogen at 0 °C $PhICl_2$ (4.41 g, 16.05 mmol) was added in one portion. After 20 min at 0 °C a solution of 2-bromophenol (2.31 g, 1.55 mL, 13.37 mmol) in CH_2Cl_2 (10 mL) was added. After stirring the mixture for 45 min at 0 °C the salts were filtered and the solvent evaporated. The crude mixture was purified by silica gel flash chromatography (hexane-EtOAc 5:1→2:1) to yield **1** (2-bromo-4-thiocyanatophenol) (1031 mg, 33%) as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.72 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.6, 2.2 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 5.78 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.4, 138.3, 134.4, 119.1, 115.3, 112.9, 112.6.

MS *m/z* 229 (M-1).

(ii) Acetic acid 4-acetylsulfanyl-2-bromo-phenyl ester

A mixture of **1** (615 mg, 2.67 mmol) and $Na_2S \cdot 9H_2O$ (706 mg, 2.94 mmol) in MeCN (25 mL) was heated at 80 °C for 1h. After cooling to 23 °C acetic anhydride (1.3 mL, 13.35 mmol) was added and the reaction stirred at 23 °C for 1h. The solution was diluted with brine and extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated. Purification by silica gel flash chromatography afforded **2** (acetic acid 4-acetylsulfanyl-2-bromo-phenyl ester) (630 mg, 82%) as a yellow oil.

^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.67 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 193.3, 168.6, 149.6, 139.1, 134.9, 127.4, 124.7, 117.1.

MS *m/z* 290 (M+1).

(iii) Acetic acid 4-thio-2-bromo-phenyl ester

To a solution of **2** (630 mg, 2.18 mmol) in MeOH (20 mL) sodium thiomethoxide (153 mg, 1M in MeOH, 2.18 mmol) was added at 23 °C. After stirring for 1 h the reaction was poured over an aqueous solution of HCl 5% and extracted with CH_2Cl_2, dried (Na_sSO_4) and evaporated to yield **3**. The crude **3** (530 mg) was used in the next reaction.

^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 2.34 (s, 3H).

MS *m/z* 246 (M-1).

(iv) 2-Bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-*(exo)*-ylsulfanyl)-phenol

A mixture of crude **3** (530 mg, 2.14 mmol), methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (470 mg, 2.14 mmol) and K_2CO_3 (593 mg, 4.36 mmol) in acetone (50 mL) was heated at 65 °C for 20 h the mixture was diluted with brine and extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated. The crude was purified first by C18 silica gel cartridges ($H_2O \rightarrow H_2O$-MeOH$\rightarrow$MeOH) and finally by reverse phase HPLC to yield 2-bromo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol (174 mg, 22%) as a white solid.

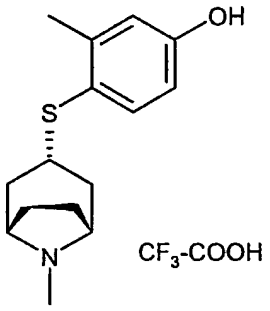
^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.62 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.87-3.84 (m, 2H), 3.31 (sp, J = 5.1 Hz, 1H), 2.70 (s, 3H), 2.31-2.24 (m, 2H), 2.12-1.85(m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.0, 141.2, 137.4, 123.9, 118.2, 111.5, 65.9, 39.7, 38.6, 37.7, 25.3.

MS *m/z* 329 (M+1).

Example 19

3-Methyl-4-(8-methyl-8-aza-bicyclo[3,2,1]oct-3-*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt



(i) 3-methyl-4-thiocyanato-phenol

To an ice-cooled suspension of $Pb(SCN)_2$ (4.48 g, 13.9 mmol) in dry methylene chloride (100 mL), $PhICl_2$ (3.04 g, 11.1 mmol), prepared according to D. Koyuncu et al., *J. Chem. Res. (S)* **1990**, 21, was added and the resulting mixture was stirred for 40 min at 0°C under nitrogen. M-cresol (1 g, 1 mL, 9.2 mmol) was added. The mixture was stirred at room temperature for 2h, and filtered through a celite pad washing extensively with methylene chloride. After addition of silicagel to the filtrate and evaporation of solvents, the mixture was purified by flash chromatography (10% ethyl acetate/hexane) to afford 1.48 g (97%) of the title compound.

Ion Electrospray Mass Spectrum M-1: 164.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.50 (d, J= 5.8 Hz, 1 H), 6.81 (d, J= 1.8 Hz, 1 H), 6.72 (dd, J= 5.8 Hz, 1.8 Hz, 1 H), 5.18 (br s, OH), 2.50 (s, 3 H);

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 157.3, 142.3, 135.0, 117.6, 113.9, 111.8, 110.8.

(ii) 4-Mercapto-3-methyl-phenol

To a hot (85 °C) solution of the intermediate from step (i) (1.48 g, 8.97 mmol) in absolute ethanol (60 mL) under nitrogen, sodium sulfide nonahydrate (2.60 g, 10.76 mmol) was added. The resulting mixture was stirred at 85 °C for 2 h. The mixture was cooled down, made acidic with an aqueous solution of HCl (10%) and extracted with methylene chloride. The organic layer was washed once with water and brine, dried on $MgSO_4$ anhydrous and concentrated in vacuo to give the title compound impurified with its disulfide (1.23 g). The mixture was quickly submitted to the next reaction without further treatment.

Ion Electrospray Mass Spectrum M-1: 139.

(iii) 3-Methyl-4-(8-methyl-8-aza-bicyclo[3,2,1]oct-3-*(exo)*-ylsulfanyl)-phenol

To a solution of intermediate from step (ii) (1.23 g, 8.80 mmol) and methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (1.73 g, 7.92 mmol) in dry dimethylformamide (30 mL) under nitrogen, potassium carbonate anhydrous (6.10 g, 44.0 mmol) was added. The resulting mixture was vigorously stirred at room temperature for 18 h under nitrogen. The mixture was filtered and the solvent was removed in vacuo. The residue was was purified by reverse phase HPLC to obtain the title compound (10.2 mg, 0.5 %).

Ion Electrospray Mass Spectrum M+1: 264.

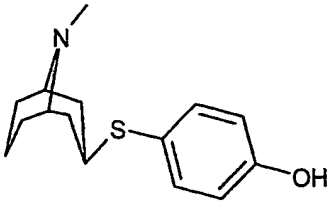
IR (cm^{-1}): 3200-3000, 1674, 1593, 1237, 799.

^1H NMR (200 MHz, CD_3OD) δ (ppm): 7.32 (d, *J*= 8.2 Hz, 1 H), 6.72 (d, *J*= 2.8 Hz, 1 H), 6.60 (dd, *J*= 8.2 Hz, 2.8Hz, 1 H), 3.82 (br m, 2 H), 3.20 (m, 1 H), 2.71 (s, 3 H), 2.41 (s, 3 H), 2.26 (m, 2 H), 2.10-1.85 (m, 6 H)

^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 160.5, 145.9, 139.9, 122.2, 119.3, 115.7, 66.4, 40.1, 39.3, 37.9, 25.7, 22.4

Example 20

4-(9-Methyl-9-aza-bicyclo[3,3,1]non-3*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt



(i) 9-Methyl-9-aza-bicyclo[3,3,1]nonan-3-*(endo)*-ol

To a –78°C cooled solution of pseudopelletierine (771 mg, 5.04 mmol), obtained from its chloro hydrate (pseudopelletierine chloride, commercially available) by treatment with saturated aqueous solution of $NaHCO_3$, extracted with methylene chloride, and dried; in THF anhydrous (20 mL), a solution 1.0 M of DIBAL-H in hexane or toluene (10.8 mL, 10.8mmol) was added dropwise under N_2. The mixture was stirred and allowed to reach rt. for 3h. The reaction was quenched with water (2mL) and poured into diethyl ether (60 mL). $NaHCO_3$ anhydrous (20 g) and Na_2SO_4 anhydrous (20 g) were added. The mixture was stirred for 2h at rt., and then, it was filtered and the filtrate was evaporated. The residue was the title compound pure, 684 mg, 88%.

Ion Electrospray Mass Spectrum M+1: 156.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.16 (m, 1 H), 2.95 (br m, 2 H), 2.40-2.20 (m, 2 H), 2.00-1.80 (m, 3 H), 1.40-1.25 (m, 3 H), 1.20-1.05 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 62.9, 51.6, 40.4, 34.8, 24.9, 14.4

(ii) 3-*(endo)*-Hydroxy-9-aza-bicyclo[3,3,1]nonane-9-carboxylic acid methyl ester

To a solution of the intermediate from step (i) (615 mg, 3.97 mmol) in dry chloroform (115 mL), methyl chloroformate (1.8 mL, 23.8 mmol) followed by potassium carbonate (457 mg, 4.56 mmol) were added. The mixture was heated at 80°C and stirred under N_2 overnight. The reaction was cooled down, quenched with water (10 mL) and extracted with chloroform. The organic layer was dried on $MgSO_4$ anhydrous, and the solvent was removed in vacuo. The residue (800 mg) was purified by flash chromatography (30% ethyl acetate/hexane) to give the title compound, 200mg, 25%.

Ion Electrospray Mass Spectrum M+1: 200.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.34 (br d, 2 H), 3.56 (s, 3 H), 3.53 (m, 1 H), 2.21 (m, 2 H), 2.17 (m, 1 H), 1.50-1.30 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 62.9, 51.6, 40.4, 34.8, 24.9, 14.4

(iii) 3-*(endo)*-Methanesulfonyloxy-9-aza-bicyclo[3,3,1]nonane-9-carboxylic acid methyl ester

To an ice-cooled solution of the intermediate from step (ii) (200 mg, 1.0 mmol) in methylene chloride anhydrous, pyridine anhydrous (0.073 mL, 0.9 mmol) followed by methanesulfonate chloride (0.085 mL, 1.1 mmol) were added under N_2. The mixture was stirred overnight and allowed to reach rt. The reaction was quenched with an aqueous solution of NH_4OH (15%), and extracted with methylene chloride. The organic layer was washed with brine and dried. The solvent was removed in vacuo to give the title compound, 210 mg, 76%.

Ion Electrospray Mass Spectrum M+1: 278.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.63 (m, 1 H), 4.50 (br m, 2 H), 3.64 (s, 3 H), 2.99 (s, 3 H), 2.42 (m, 2 H), 1.80-1.60 (m, 8 H).

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 156.0, 74.5, 52.5, 45.0, 38.5, 32.4, 29.6, 14.0

(iv) 3-(*exo*)-(4-Hydroxy-phenylsulfanyl)-9-aza-bicyclo[3,3,1]nonane-9-carboxylic acid methyl ester

To a solution of the intermediate from step (iii) (107.1 mg, 0.39 mmol) and 4-mercaptophenol (98.3 mg, 0.78 mmol) in dry DMF (25 mL), ceasium fluoride (118.5 mg, 0.78mmol) was added. The mixture was heated at 60°C and stirred overnight under N_2. The reaction was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and dried. The solvent was removed in vacuo to give the title compound, which was submitted to the next reaction without further treatment.

Ion Electrospray Mass Spectrum M+1: 308, M-1: 306.

(v) 4-(9-Methyl-9-aza-bicyclo[3,3,1]non-3-*(exo)*-ylsulfanyl)-phenol, trifluoroacetate salt

To an ice-cooled solution of the intermediate from step (iv) (119.7 mg, 0.39 mmol) in ethyl ether anhydrous (THF anhydrous can be used too) (2 mL), lithium aluminium hydride (LAH) (74 mg, 1.95 mmol) was added. The mixture was stirred overnight under N_2 and allowed to reach rt. The reaction was quenched with water and methanol at 0°C

(violent reaction), and filtered. The filtrate was evaporated and the residue was submitted to SCX collecting the desired product slightly impurified, which was purified by reverse phase HPLC to obtain the title compound, 30 mg, 21%.

The structural analysis was done with the ammonium salt and the free amine.

Ion Electrospray Mass Spectrum M+1: 264, M-1: 262

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) for the free amine: 7.38 (d, *J*= 8.6 Hz, 2 H), 6.75 (d, *J*= 8.6 Hz, 2 H), 3.68 (m, 1 H), 3.50 (br s, 2 H), 2.82 (s, 3 H), 2.25-2.15 (m, 6 H), 2.03-1.85 (m, 3 H), 1.60 (m, 1 H).

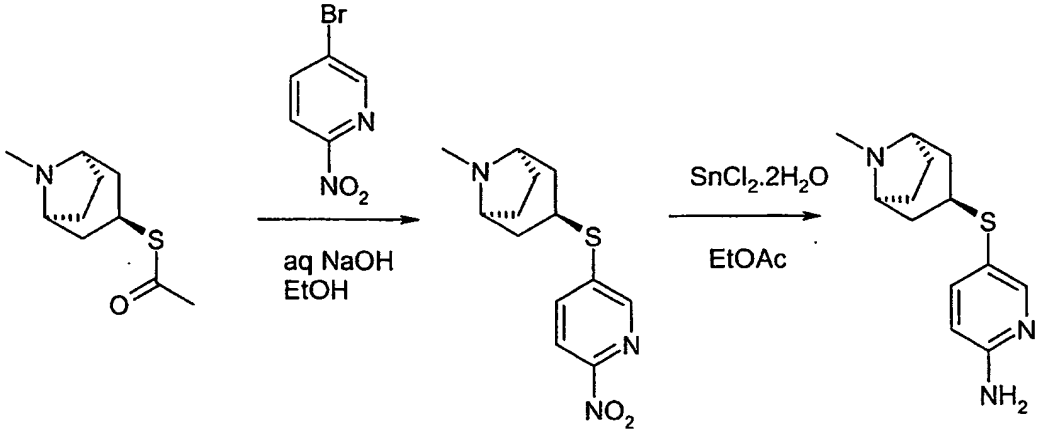
^{13}C NMR (150 MHz, CD_3OD) δ (ppm) for the ammonium salt. Two N-methyl invertomers were detected depending on the N-methyl position. Both are described:

A: 158.6, 137.2, 120.6, 115.9, 56.2, 38.8, 37.9, 36.9, 20.9, 17.8.

B: 158.5, 136.9, 120.3, 115.9, 55.7, 38.5, 36.9, 29.2, 28.8, 17.5.

Example 21

5-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]-2-pyridinylamine



(i) 8-methyl-3-[(6-nitro-3-pyridinyl)thio]-8-azabicyclo[3.2.1]octane.

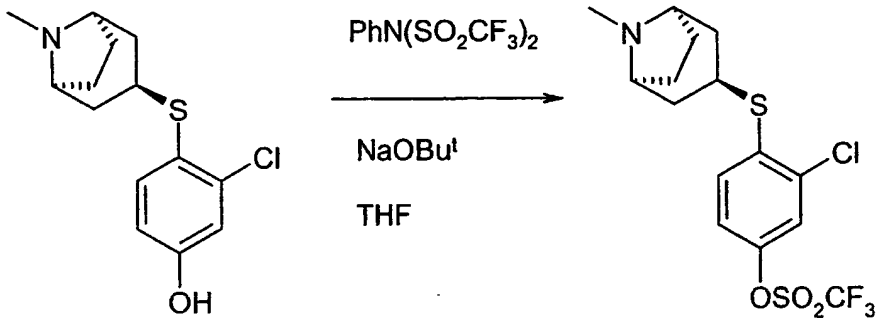
A mixture of (8-methyl-8-azabicylo[3.2.1]oct-3-yl)ethanethioate (1.24 g) and 2-nitro-5-bromopyridine (790 mg) in ethanol (15 ml) and aqueous sodium hydroxide (2M, 2 ml) was stirred at room temperature overnight. The mixture was applied directly to an SCX cartridge and eluted sequentially with methanol then 2M ammonia in methanol to yield the crude product (500 mg). This was purified by preparative LC-MS to yield 8-methyl-3-[(6-nitro-3-pyridinyl)thio]-8-azabicyclo[3.2.1]octane (50 mg).

(ii) 5-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]-2-pyridinylamine.

A mixture of 8-methyl-3-[(6-nitro-3-pyridinyl)thio]-8-azabicyclo[3.2.1]octane (50 mg) and tin (II) chloride dihydrate (202 mg) in ethyl acetate was heated under reflux for 4 days and the worked up by quenching with aqueous sodium hydrogen carbonate solution. The product was extracted into ethyl acetate and the organic layer dried, filtered and concentrated to yield the crude aminopyridine (30 mg). The material was cleaned up on an SCX cartridge as above to yield 5-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]-2-pyridinylamine (25 mg).

Example 22 (intermediate preparation)

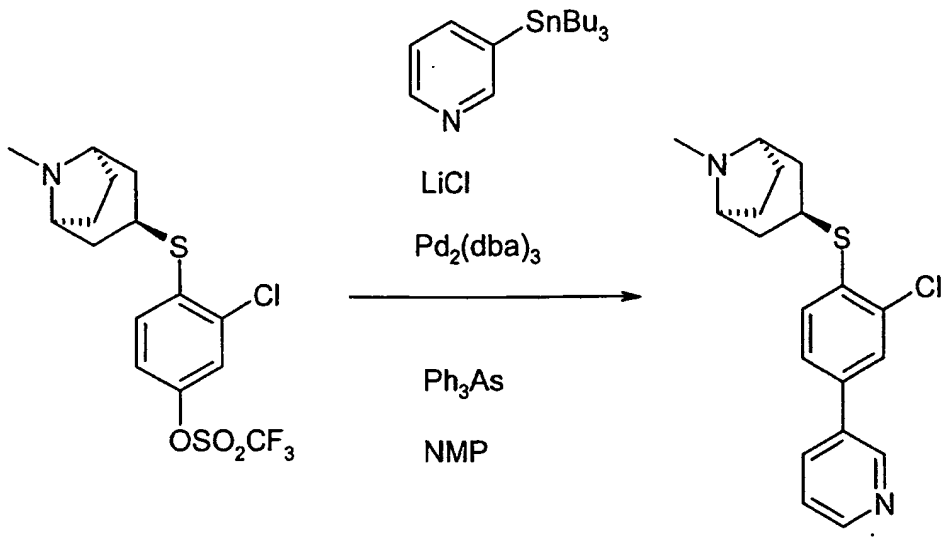
3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate



3-Chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenol (Example 72, 274 mg) was dissolved in anhydrous THF (10 ml) under nitrogen and cooled to 0 °C. To this was added in one portion sodium tert-butoxide (97 mg) and the solution stirred for 10 minutes. The flask was removed from the ice-bath and N-phenyltrifluoromethanesulfonimide (750 mg) added. The solution was stirred at room temperature overnight. Water was added and the layers separated. The aqueous phase was extracted with ethyl acetate and the combined organics washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered and evaporated to dryness. The material was purified on an SCX cartridge eluting sequentially with methanol then 2M ammonia in methanol to provide 3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate (192 mg).

Example 23

a) **3-{[2-chloro-4-(3-pyridinyl)phenyl]thio}-8-methyl-8-azabicylo[3.2.1]octane**



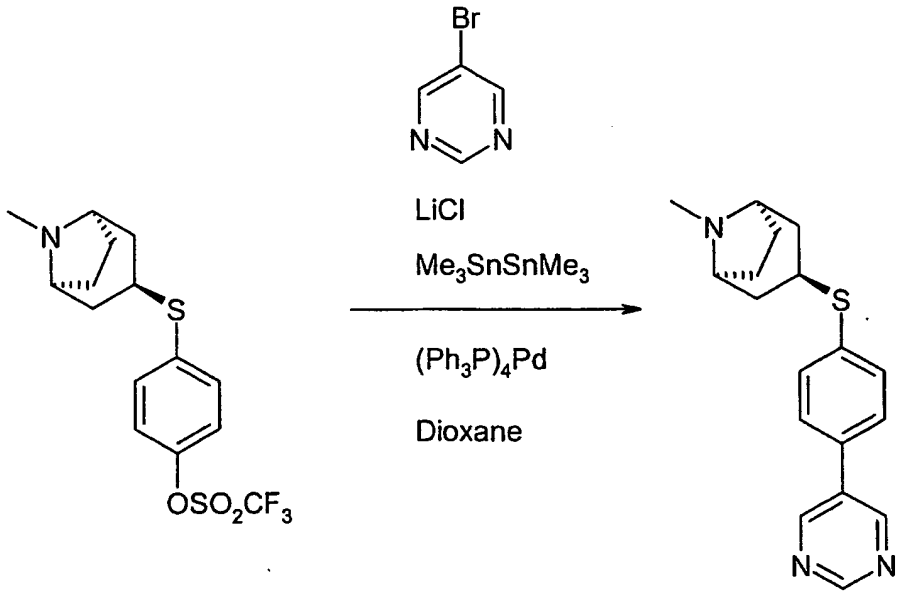
A mixture of 3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate (215 mg), lithium chloride (70 mg), triphenylarsine 32 mg) and tris(dibenzylideneacetone)-dipalladium (0) (20 mg) was stirred in N-methylpyrrolidinone (10 ml) under nitrogen for 5 minutes. To this was added 3-tributylstannylpyridine (200 mg) and the solution heated to 100 °C for 2 hours. The solution was cooled to room temperature and aqueous sodium hydroxide (10%) added to quench the reaction. The mixture was extracted three times with dichloromethane, the combined organics dried ($MgSO_4$), filtered and evaporated to dryness. The material was purified on an SCX cartridge eluting sequentially with methanol and 2M ammonia in methanol, followed by preparative LC-MS yielding 3-{[2-chloro-4-(3-pyridinyl)phenyl]thio}-8-methyl-8-azabicylo[3.2.1]octane (54 mg)

b) 8-methyl-3-{[4-(3-pyridinyl)phenyl]thio}-8-azabicyclo[3.2.1]octane

Also prepared by this procedure was 8-methyl-3-{[4-(3-pyridinyl)phenyl]thio}-8-azabicyclo[3.2.1]octane (from 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate and 3-tributylstannylpyridine).

Example 24

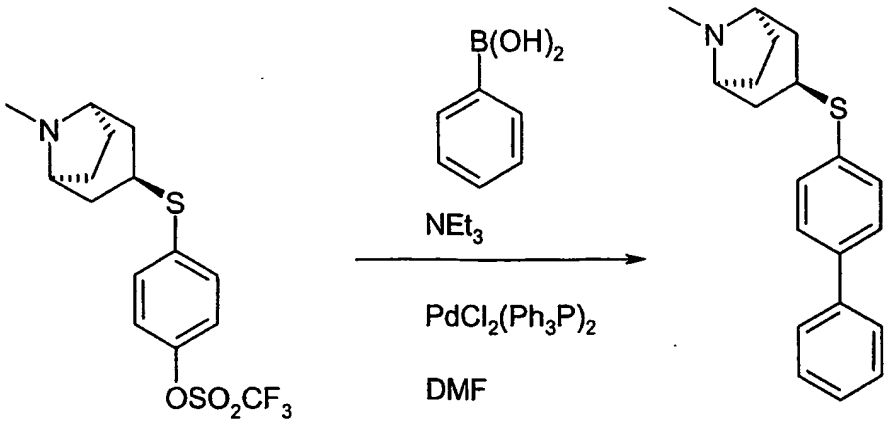
8-methyl-3-{[4-(5-pyrimidinyl)phenyl]thio}-8-azabicyclo[3.2.1]octane



To a mixture of 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate (450 mg), 5-bromopyrimidine (187 mg), lithium chloride (150 mg) and tetrakis(triphenylphosphine) palladium (0) (68 mg) under nitrogen were added hexamethylditin (386 mg) and dioxane (15 ml). The mixture was heated under reflux overnight and then poured into a mixture of aqueous potassium fluoride (1.9g in 13 ml water) and ethyl acetate (13 ml). This mixture was stirred vigorously for 2 hours, passed through a sintered funnel and the layers separated. The organic phase was washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude material was purified on an Isco CombiFlash device, followed by UV-guided LC to yield 8-methyl-3-{[4-(5-pyrimidinyl)phenyl]thio}-8-azabicyclo[3.2.1]octane (45 mg)

Example 25

a) [1,1'-biphenyl]-4-yl 8-methyl-8-azabicyclo[3.2.1]oct-3-yl sulfide



To a mixture of 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate (0.4 g) and phenylboronic acid (0.25 g) in DMF (5 ml) were added triethylamine (0.58 ml) followed by dichlorobis(triphenylphosphine) palladium (II) (0.04 g). The solution was heated at 90 °C for 4 hours, cooled to room temperature and diluted with ethyl acetate. This was washed with saturated aqueous sodium hydrogen carbonate solution, then brine, dried ($MgSO_4$), filtered and evaporated. Partial clean up was achieved using preparative LC-MS. The mixture was stirred with aqueous sodium hydroxide solution (0.5M) to hydrolyse residual triflate to the phenol. The product was extracted into ethyl acetate, still however contaminated with some of the phenol. The material was loaded onto a PE-AX column and eluted with methanol with the final clean up by preparative LC-MS to yield [1,1'-biphenyl]-4-yl 8-methyl-8-azabicyclo[3.2.1]oct-3-yl sulfide.

Also prepared by this procedure from 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl trifluoromethanesulfonate and the appropriate arylboronic acid were:

b) N-{4'-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio][1,1'-biphenyl]-3-yl}acetamide

c) 8-methyl-3-{[4-(3-pyridinyl)phenyl]thio}-8-azabicyclo[3.2.1]octane

d) 3-{[2',4'-dichloro(1,1'-biphenyl]-4-yl]thio}-8-methyl-8-azabicylo[3.2.1]octane

e) 3-{[4-(1-benzofuran-2-yl)phenyl]thio}-8-methyl-8-azabicylo[3.2.1]octane

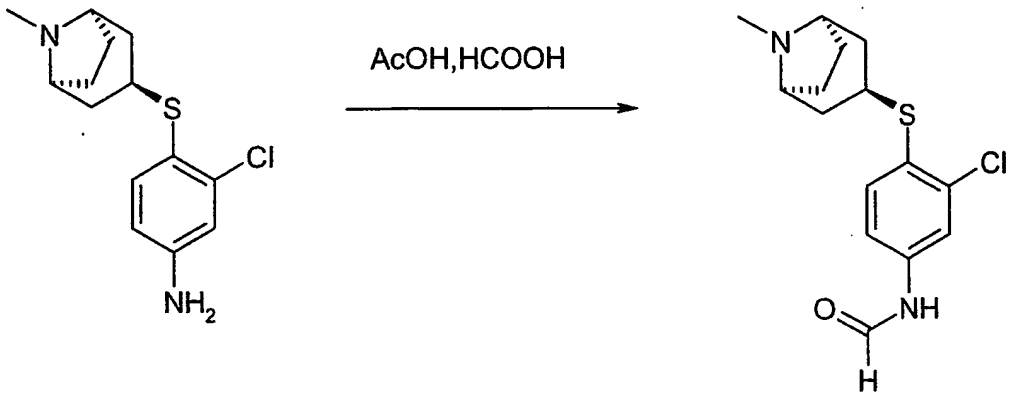
f) 3-{[4-(5-carboxamido-3-pyridinyl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane

g) 3-{[4-(3-carboxamido-phenyl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane

h) 3-{[4-(3,4,5,6-dehydro-2-oxo-piperidin-5-yl)phenyl]thio}-8-methyl-8-azabicyclo[3.2.1]octane

Example 26

a) 3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylformamide



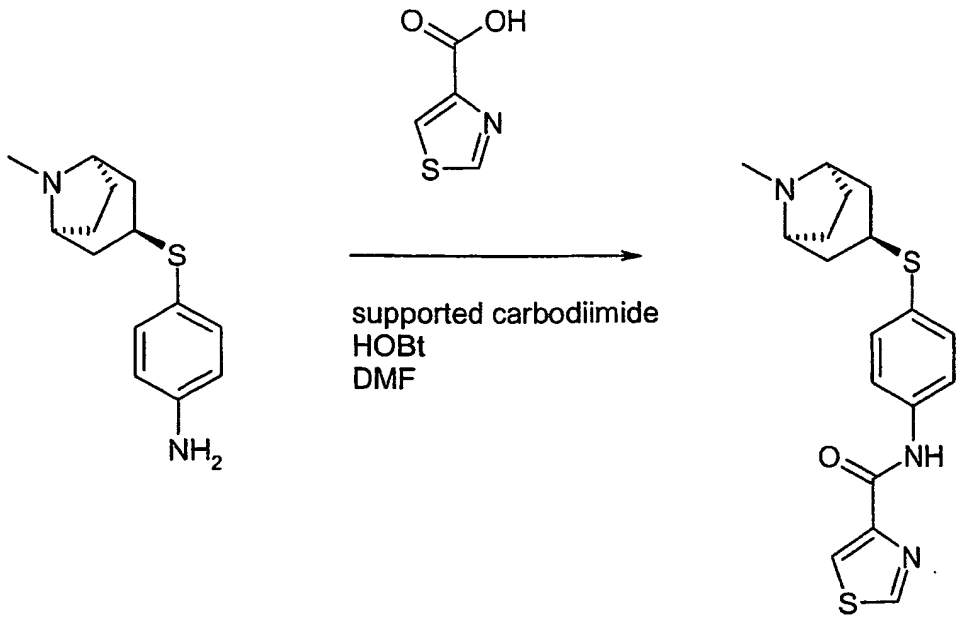
A mixture of acetic acid (0.96 g) and formic acid (0.53 g) was heated under reflux for 2 hours. To this was added 3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylamine (265 mg) and heating continued for 1.5 hours. The crude mixture was placed on an SCX cartridge and eluted with methanol followed by 2M ammonia in methanol. The impure product was then subjected to flash chroamtography on silica gel (gradient elution with increasing percentage of methanol in chloroform) to yield material of 93% purity. Final clean up by preparative LC-MS gave 3-chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylformamide (40 mg)

b) 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylformamide

Prepared in an analogous manner was 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylformamide.

Example 27

a) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-4-thiazolecarboxamide



A mixture of 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylamine (50 mg), 4-carboxythiazole (52 mg), 1-hydroxybenzotriazole (61 mg) and carbodiimide resin (1.7 mmol/g, 470 mg) in DMF (7 ml) was stirred at room temperature for 3 days. The mixture was filtered then passed through an SCX cartridge, eluting with methanol followed by 2M ammonia in methanol, providing N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-4-thiazolecarboxamide as a white solid (55 mg)

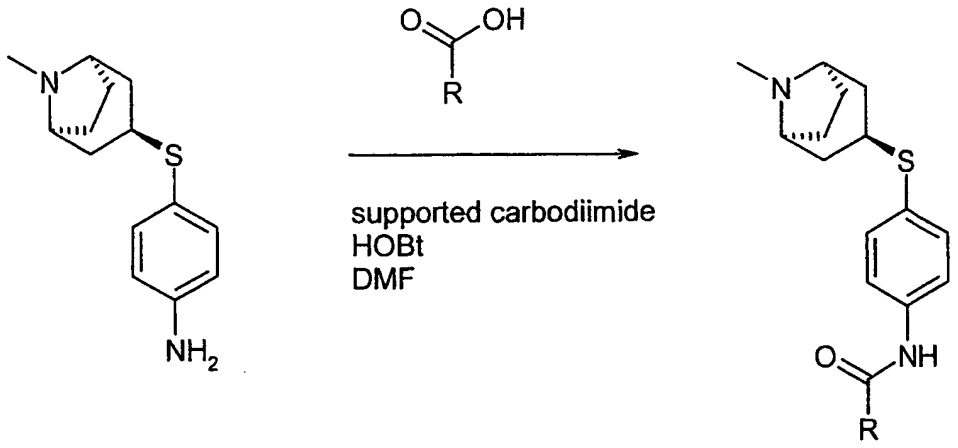
Prepared in a similar fashion were:

b) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-1,2,3-thiadiazole-4-carboxamide

c) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-thiophenecarboxamide

d) N-{3-Chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-thiophenecarboxamide

Example 28



Stock solutions of 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenylamine ("the substrate", 0.05M), 1-hydroxybenzotriazole ("the reagent", 0.1M) and a set of 24 carboxylic acids ("the monomers", 0.1M) were all prepared in DMF. Each well of a 24-well RPS plate was loaded with carbodiimide resin (loading 1.7 mmol/g, 59 mg) and then each treated with 0.5 ml of the substrate solution, the reagent solution and a monomer solution. These were stirred at room temperature for 72 hours, filtered from the resin, passed through SCX cartridges eluting with methanol then 2M ammonia in methanol and concentrated. The materials were then further purified by preparative LC-MS to provide the carboxamides in an average yield of 67%

By this method were prepared:

a) **N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]benzamide**

b) **N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-4-nitrobenzamide**

c) **4-Methoxy-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]benzamide**

d) **4-Isopropyl-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]benzamide**

e) **4-Chloro-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]benzamide**

f) **4-Methyl-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]benzamide**

g) **N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-2-phenylacetamide**

h) **N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-2-(4-methylphenyl)acetamide**

i) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-2-(4-methoxyphenyl)acetamide

j) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-2-(4-fluorophenyl)acetamide

k) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-phenylpropanamide

l) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-4-phenylbutanamide

m) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]propanamide

n) 2-Methyl-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]propanamide

o) 2,2-Dimethyl-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]propanamide

p) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]butanamide

q) 3,3-Dimethyl-N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]butanamide

r) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-butenamide

s) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]cycohexanecarboxamide

t) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]cyclopentanecarboxamide

u) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-2-pyridinecarboxamide

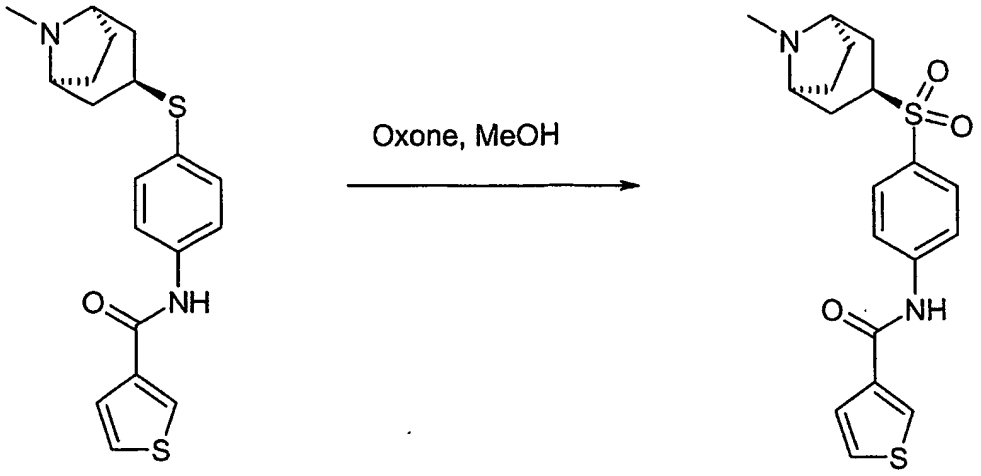
v) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-pyridinecarboxamide

x) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-thiophenecarboxamide

y) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-indolecarboxamide

Example 29

a) N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)sulfonyl]phenyl]-3-thiophenecarboxamide



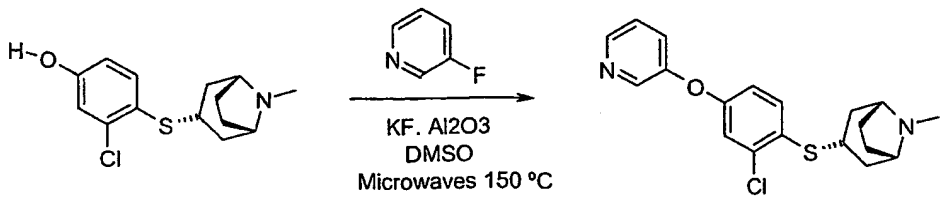
To a solution of N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenyl]-3-thiophenecarboxamide (130 mg) in methanol (5 ml) was added a solution of Oxone (446 mg) in water. The mixture was stirred at room temperature for 30 minutes and then applied directly to an SCX cartridge. The impure product eluted with methanol and was subjected to further clean up by preparative LC-MS to yield N-{4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)sulfonyl]phenyl]-3-thiophenecarboxamide (75 mg).

b) 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)sulfonyl]phenylformamide

Prepared in a similar manner was 4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)sulfonyl]phenylformamide

Example 30

3-(*exo*)-[2-Chloro-4-(pyridin-3-yloxy)-phenylsulfanyl]-8-methyl-8-azabicyclo [3.2.1]octane

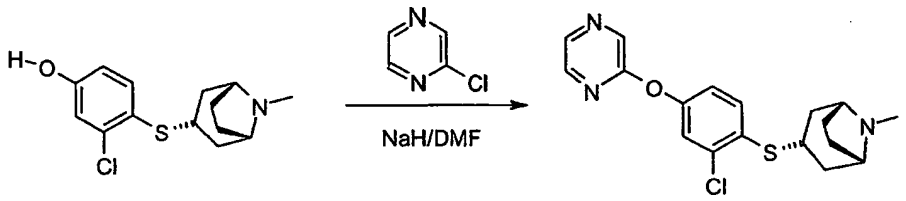


A mixture of 3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol (Example 72, 1.0 eq), 3-fluoropyridine (1.0 eq) 18-crown-6 (1 eq) and 37% w/w potassium-fluoride alumina in DMSO , was treated under microwaves conditions at 150 °C over 1 hour. Dichloromethane was added to the mixture reaction and then the organic layer was washed with water. Separated and dry over Mg_2SO_4 and concentrated to give a crude product which was purified by chromatroton silicagel rotors.

MS (ES)$[M+H]^+$: 361.1

Example 31

3-(*exo*)-[2-Chloro-4-(pyridin-2-yloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

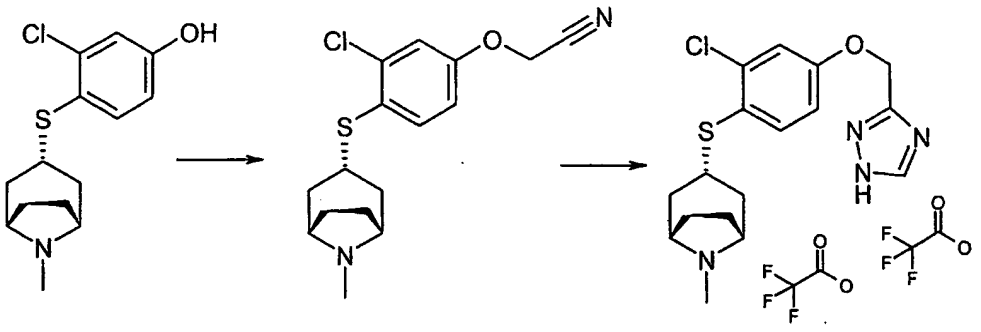


To a suspension of NaH 60% (0.020 g, 0.51 mmol) in DMF anh. (2.5 ml), 3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol (0.050 g, 0.17 mmol) was added and the mixture reaction stirred 15 min. Then 2-chloropyrazine (0.019g, 0.17 mmol) was added and the mixture reaction was refluxed for 3 h.. After cooling the mixture was treated with CH_2Cl_2 and washed with water and brine. The organic phase was dry over $MgSO_4$ and concentrated in vacuo. The crude was purified in silicagel to give the desired product.

MS (ES)$[M+H]^+$: 363

Example 32

(a) 3-(*exo*)[2-Chloro-4-(1*H*-[1,2,4]triazol-3-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane, bis trifluoroacetic acid salt



(i) [3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-acetonitrile

To a solution of phenol (XX) (1 g, 3.53 mmol) in dry dimethylformamide (34 mL) at r.t. under nitrogen, cesium carbonate (2.3 g, 7.06 mmol) was added. The mixture was stirred for 15 min and then chloroacetonitrile (0.225 mL, 3.6 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 3 h and was diluted with methylene chloride. The resulting mixture was washed with water and the aqueous phase extracted with methylene chloride (x3). The combined organic phase was dried over sodium sulfate, filtered and evaporated to dryness to obtain 1.1 g (97%) of titled compound which was submitted directly to the next reaction.

EI-MS: 323 (M+1)

^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.55 (d, *J*= 8.7 Hz, 1 H), 7.21 (d, *J*= 2.8 Hz, 1 H), 7.00 (dd, *J*= 8.7, 2.8 Hz, 1 H), 5.01 (s, 2H), 3.42 (sept, *J*= 8.9 Hz, 1 H), 3.20 (br s, 2 H), 2.26 (s, 3H), 2.08 (m, 2 H), 1.79 (d, J= 2.8 Hz, 2 H), 1.7 (d, J= 2.0 Hz, 2 H), 1.64 (d, *J*= 8.5 Hz, 2H).

^{13}C NMR (300 MHz, CD_3OD) δ (ppm) 158.3, 139.6, 127.6, 117.8, 116.6, 115.2, 115.4, 62.8, 54.6, 39.8, 38.9, 38.6, 26.6.

(ii) 3-(*exo*)[2-Chloro-4-(1*H*-[1,2,4]triazol-3-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane, bis trifluoroacetic acid salt

To a solution of [3-Chloro-4-(*exo*)(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenoxy]-acetonitrile (0.4 g, 1.24 mmol) in methanol (0.5 mL) at 0°C under nitrogen sodium methoxide (34 mg, 0.63 mmol) was added, the resulting mixture was stirred for 30 min at that temperature and acetic acid (0.035 mL, 0.63 mmol) and formylhydrazide

(75 mg, 1.24 mmol) were successively added. The resulting mixture was stirred at r.t. for 15 min, evaporated, dissolved in dry dimethylformamide (2 mL) and heated at 115°C for 90 min. The mixture was cooled down, diluted with methylene chloride. The resulting mixture was washed with water and the organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by SPE to obtain 0.327 g (44%, 3 steps) of titled compound.

EI-MS: 365 (M+1)

^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 8.42 (s, 1 H), 7.55 (d, *J*= 8.7 Hz, 1 H), 7.24 (d, *J*= 2.6 Hz, 1 H), 7.00 (dd, *J*= 8.7, 2.8 Hz, 1 H), 5.21 (s, 2H), 3.88 (br s, 2 H), 3.50 (sept, *J*= 5.8 Hz, 1 H), 2.72 (s, 3H), 2.32-1.95 (m, 8 H).

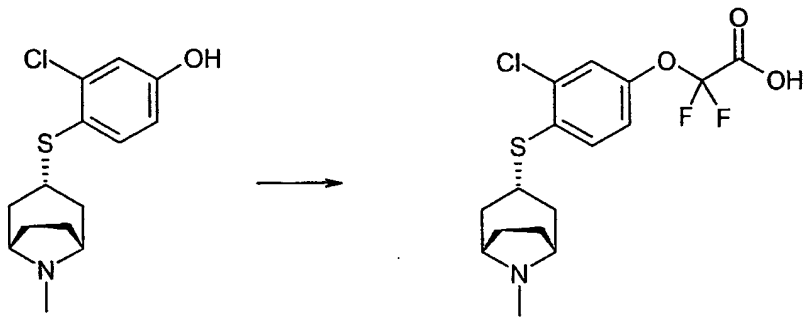
^{13}C NMR (300 MHz, CD_3OD) δ (ppm) 160.7, 158.4, 147.0, 140.5, 138.6, 124.1, 117.9, 115.4, 65.0, 64.0, 38.9, 37.8, 36.9, 25.1.

(b) 3-(*exo*)[2-chloro-4-(1*H*-[1,3,4]oxadiazol-2-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane trifluoroacetic acid salt

By proceeding in a similar manner to Example 32(a) but using ethyl bromoacetate in step (i), there was prepared 3-(*exo*)[2-chloro-4-(1*H*-[1,3,4]oxadiazol-2-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane trifluoroacetic acid salt.

Example 33

[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-difluoro-acetic acid



(i) [3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-difluoro-acetic acid

To a solution of phenol (XX) (1 g, 3.53 mmol) in dry dioxane (12 mL) at 0°C under nitrogen sodium hydride (2.1 g, 88.25 mmol) and chlorodifluoroacetic acid (3 mL, 35.27 mmol) were successively added. The resulting mixture was heated at reflux for two days and cooled down to 0°C. To the cold mixture ice-water was added carefully, and the resulting mixture was evaporated in vacuo. diluted with a solution of hydrochloric acid (10%) and extracted with methylene chloride (x2). The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by SCX to obtain 0.433 g (32%) of titled compound.

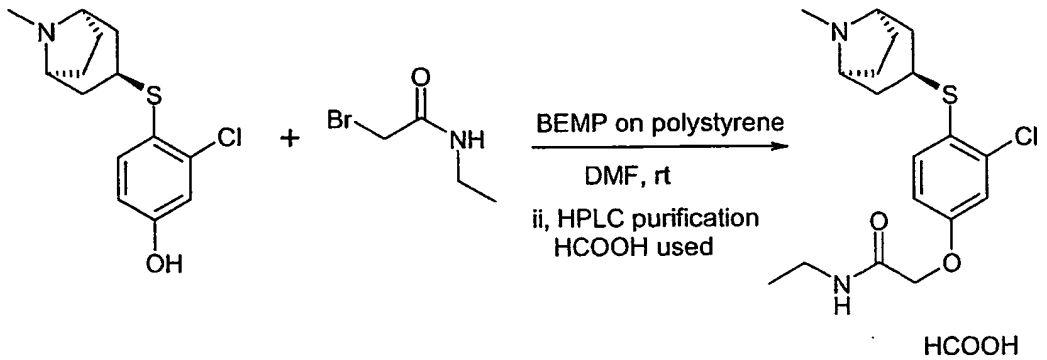
EI-MS: 378 (M+1)

^{1}H NMR (200 MHz, CD_3OD) δ (ppm) 7.58 (d, *J*= 8.6 Hz, 1 H), 7.37 (d, *J*= 2.4 Hz, 1 H), 7.19 (dd, *J*= 8.6, 2.6 Hz, 1 H), 3.88 (br s, 2 H), 3.60 (sept, *J*= 6.0 Hz, 1 H), 2.74 (s, 3H), 2.32-1.91 (m, 8 H).

^{13}C NMR (300 MHz, CD_3OD) δ (ppm) 164.2 (d, *J*= 34.2 Hz), 151.8, 137.9, 135.7, 128.2, 122.6, 120.2, 116.7 (t, *J*= 450 Hz), 64.4, 38.2, 36.9, 35.2, 23.9.

Example 34

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-ethyl-acetamide, formic salt



(i) 2-bromo-N-ethyl-acetamide

To a solution of ethylamide (0.056 mL, 1 mmol) plus triethylamine (0.4 mL, 2.9 mmol) in dry DCM (5 mL), bromoacetyl-bromide (0.2 mL, 2.3 mmol) was added at –78°C under N_2 atmosphere (exotermic reaction). The mixture was stirred and allowed to reach room temperature until the starting material had disappeared by TLC (eluent:

DCM/MeOH/NH_4OH drops, UV as developer, dark brown colour). The reaction was quenched with an aqueous solution of $NaHCO_3$ (5%). Both phases were stirred vigorously, and then they were separated with a column (empty cartridge) with hydrophobic resin 5 micros called FPTE (12mL capacity). The organic layer was collected in a 13/100 tube and the solvent was evaporated in the N_2 stream. The residue was dissolved in dry DMF (2mL) to have a solution of 2-bromo-N-ethyl-acetamide 0.5N to use in next step.

(ii) 2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-ethyl-acetamide, formic salt

To a suspension of 3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol (50 mg, 0.18 mmol) plus 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine (BEMP) on polystyrene (2.2 mmol base / g) (509mg, 1.08 mmol) in dry DMF (1 mL) in a glass vial charged with two caps and with a polystyrene frit., a solution of 2-bromo-N-ethyl-acetamide (0.5N in DMF) (0.36 mL, 0.18 mmol) made in the step i, was added at room temperature. The mixture was stirred for 16h and checked by MS. The reaction solution was filtered and the resin was washed with MeOH several times. The combined organic fractions (DMF plus MeOH) were evaporated and the residue (45 mg) was submitted to HPLC purification (preparative LC-MS) collecting the title compound (10 mg)

MS (ES) [M+1]: 368

^1H NMR δ (ppm) (200 MHz, MeOD): 8.48 (br s, H-COOH, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 6.93 (dd, J = 2.9, 8.9 Hz, 1H), 4.49 (s, 2H), 3.82 (m, 2H), 3.49 (m, 1H), 3.28 (m, 2H), 2.69 (s, 3H), 2.30-1.90 (m, 8H), 1.12 (t, J = 7.3 Hz, 3H)

Prepared in a similar fashion were prepared the formic salts of:

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N,N-diethyl-acetamide,

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-isopropyl-acetamide,

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-cyclohexyl-acetamide,

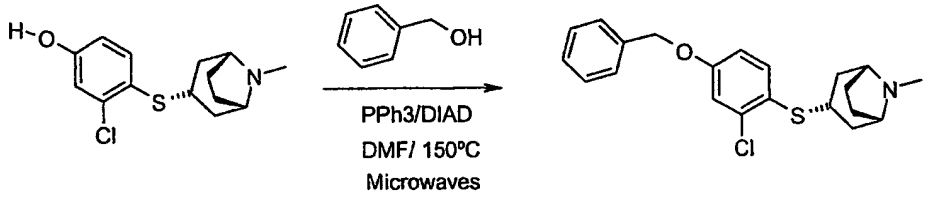
N-Benzyl-2-[3-chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-acetamide,

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-(4-fluoro-benzyl)-acetamide,

2-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenoxy]-N-(2,4-difluoro-benzyl)-acetamide,

Example 35

3-(*exo*)-(4-Benzyloxy-2-chloro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane



3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol (0.050g, 0.17 mmol), PPh_3P (0.129 g, 0.49mmol), and benzylic alcohol (0.026 ml, 025.mmol) were dissolved in DMF and to this solution DIAD was added (0.088g, 0.44 mmol). The mixture reaction was treated at 150 °C under microwaves conditions over 3 hours. The mixture reaction dissolved in methanol was passed through a SCX cartridge then eluting 2M ammonia in methanol and concentrated. The material was then further purified by preparative LC-MS to provide the desired product.

MS (ES) $[M+H]^+$: 374.

By this method were prepared:

3-(*exo*)-[2-Chloro-4-(2-trifluoromethyl-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(3-trifluoromethyl-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(2-methoxy-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(3-methoxy-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(3-fluoro-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(3,5-difluoro-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-2-chloro-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

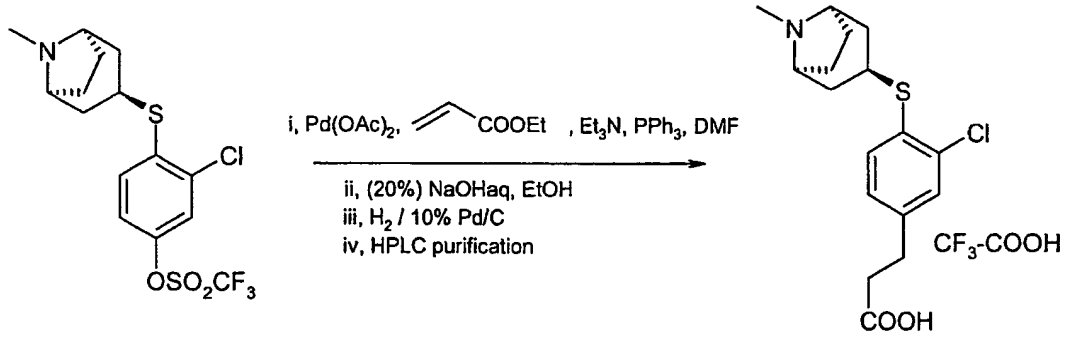
3-(*exo*)-[2-Chloro-4-(2,6-difluoro-benzyloxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(thiophen-2-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

3-(*exo*)-[2-Chloro-4-(imidazol-2-ylmethoxy)-phenylsulfanyl]-8-methyl-8-aza-bicyclo[3.2.1]octane

Example 36

3-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenyl]-propionic acid, N-trifluoroacetic salt



(i) 3-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenyl]-acrylic acid ethyl ester

To a stirred solution of trifluoro-methanesulfonic acid 3-chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenyl ester (306 mg, 0.74 mmol) in dry DMF (2 mL) under N_2 atmosphere at room temperature, were secuentially added triethylamine (0.11 mL, 0.81 mmol), ethyl acrylate (0.16 mL, 1.48 mmol), triphenylphosphine (7.87 mg, 0.03 mmol) and palladium acetate (2.24 mg, 0.01 mmol). The mixture was degassed and stirred for 2h at 100°C.

As the reaction hadn't been done by MS (ES), the duplicated quantities of the reactants were added to the reaction, degassed again, and stirred at 100°C for 48h. The reaction was quenched with water, and the solvent was removed in vacuo. The residue was dissolved in methanol and submitted to SCX cartridge. The ammonia fraction was submitted to a flash column chromatography on silica gel (using DCM/solution 2M NH_3 in MeOH) collecting the title compound mixed with starting material (150mg) and 3-chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol, product of the hydrolysis of the starting material. The mixture of starting material and the title compound was submitted to next reaction without further purification.

MS (ES) [M+1]= 366

(ii) 3-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenyl]-acrylic acid

To a solution of the intermediate from step (i) (150 mg) in ethanol (4 mL), an aqueous solution of sodium hydroxide (20%) was added at room temperature. The reaction was stirred for 16h. The reaction was checked by MS (ES), and the starting material had been converted in the title compound. Then, the solvent was removed in vacuo, and the residue was submitted to SPE cartridge using 0.05% TFA in water/ acetonitrile, collecting the title compound mixed with the 3-chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol. (123 mg)

MS (ES) [M+1] = 338

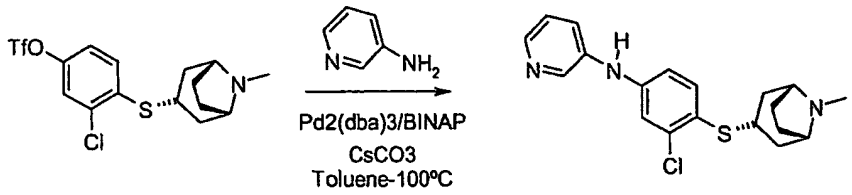
(iii) 3-[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenyl]-propionic acid. N-trifluoroacetic salt.

To a solution of the intermediate from step (ii) (123mg) in dry DMF, palladium in active carbon (10%) (820mg) was added. The mixture was degassed and stirred under hydrogen atmosphere for 16h. The solvent was removed in vacuo and the residue was submitted to SAX cartridge, and HPLC purification to get the title compound.

MS (ES) [M+1]: 339

Example 37

[3-Chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-(*exo*)-ylsulfanyl)-phenyl]-pyridin-3-yl-amine

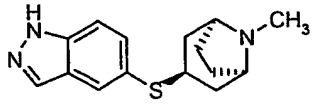


In a dry schlenk flask we charged $Pd_2(dba)_3$ (2.0 mmol/%), BINAP (2.0 mmol/%) and $CsCO_3$ (0.054 g, 0.168 mmol), evacuated and filled with Argon. Then trifluoro-methanesulfonic acid 3-chloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenyl ester (0.050 g, 0.12 mmol) and 3-aminopyridine (0.0135, 0.144 mmol) were added under Argon. Toulene was added to this mixture and the septum was replaced with a teflon screwcap heating the reaction at 100°C overnight. The reaction was concentrated to dryness and purified by chromatography in SiO_2 (CH_2Cl_2/ 2M NH_4OH/ MeOH: 9.5/0.5) to yield the desired product.

MS (ES) $[M+H]^+$: 361

Example 38

Exo-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole



(i) 1-*H*-Indazole-5-thiol

5-Aminoindazole (10g, 0.075mol) was suspended in water (150ml) and heated to 60°C. Concentrated HCl (26ml) was added to form the HCl salt and the mixture stirred at 60°C for 30 minutes before cooling to -3°C in an ice/ MeOH bath. Diazotization was performed by dropwise addition of a pre-chilled (~3°C) solution of sodium nitrite (5.18g, 0.075mol) in water (75ml), beneath the surface of the stirring solution. The temperature was maintained below 0°C for 30 minutes. Meanwhile, potassium ethyl xanthate (18.03g, 0.112mol) was dissolved in water and heated to 70°C. The diazonium species was then

added slowly to the hot solution and stirring continued at this temperature for 2 hours. The reaction mixture was allowed to cool then was extracted with diethyl ether (4 × 200ml), washed with 2N NaOH (2 × 200ml) then water (200ml) and brine (200ml). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the xanthate as a viscous brown oil (4.96g, 28%). The crude xanthate was slowly added as a solution in THF (125ml) *via* cannula to a solution of $LiAlH_4$ (75ml, 1M in THF, 0.075mol) in THF (50ml) at 0°C. Exhaust gases from this reaction were bubbled through bleach. When addition was complete, the reaction mixture was heated to reflux for 1 hour then re-cooled to 0°C and quenched by careful addition of water (86ml). The aluminium residues were then destroyed by addition of concentrated HCl (45ml). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 150ml) then the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to furnish the impure thiol as a yellow solid (2.55g, 23% over two steps); this was used immediately without further purification; LCMS retention time ~3.09min *m/z* 151.1[$(M+H)^+$, 54.6%] plus a small amount of disulfide; LCMS retention time ~4.5min 299.0 [$(M+H)^+$, 6.1%] and other impurities.

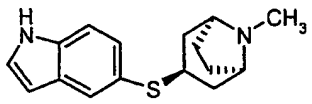
(ii) Exo-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole

1-*H*-Indazole-5-thiol (1.27g, 8.47mmol) was stirred with CsF (1.29g, 8.47mmol) and ENDO-methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (2.04g, 9.31mmol) in DMF (15ml) for 18 hours at room temperature. The mixture was then heated to 60°C for a further 24 hours. The DMF was removed by washing the reaction mixture onto an SCX-2 cartridge, washing with MeOH, then eluting the product with NH_3/ MeOH (~2M) and concentrating *in vacuo*. The crude material was purified by column chromatography (eluent; 5% MeOH in DCM) to furnish slightly impure product. This was further purified by trituration with $CHCl_3$/ ether, which afforded the title compound as an off-white solid (77mg, 3.3%);

δ_H (300MHz, $CDCl_3$); 1.61-1.68 (2H, m), 1.78-1.84 (2H, m), 1.89-1.98 (2H, m), 2.02-2.10 (2H, m), 2.24 (3H, s, NCH_3), 3.09-3.21 (1H, m, C**H**), 3.25 (2H, br s, 2 × C**H**), 7.20-7.23 (1H, m, Ar-**H**), 7.39-7.40 (1H, m, Ar-**H**), 7.89 (1H, s, Ar-**H**), 7.98 (1H, s, Ar-**H**), 11.57 (1H, br s, N**H**); LCMS retention time ~1.73, m/z 274.1 [$(M+H)^+$, 100%].

Example 39

Exo-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indole

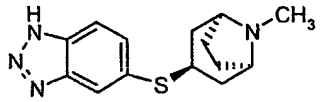


By proceeding in a similar manner to Example 38 but using 5-aminoindole there was prepared the title compound as a pale yellow solid.

δ_H (300MHz, $CDCl_3$); 1.52-1.56 (2H, m), 1.70-1.79 (2H, m), 1.80-1.89 (2H, m), 1.95-2.05 (2H, m), 2.25 (3H, s, NCH_3), 3.12-3.21 (3H, m, 3 × C**H**), 6.50 (1H, br s, Ar-**H**), 7.21-7.23 (1H, m, Ar-**H**), 7.30 (2H, s, 2 × Ar-**H**), 7.81 (1H, s, Ar-**H**), 8.72 (1H, br s, N**H**); LCMS retention time ~2.5min, m/z 273.1 $[(M+H)^+$, 100%].

Example 40

Exo-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-benzotriazole

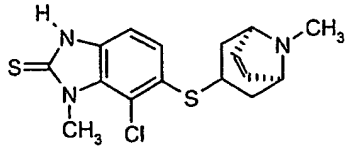


By proceeding in a similar manner to Example 38 but using 5-aminobenzotriazole there was prepared the title compound as a pale yellow solid.

δ_H (300MHz, $CDCl_3$); 1.75-1.82 (2H, m), 1.89-2.00 (2H, m), 2.08-2.22 (4H, m), 2.37 (3H, s, NCH_3), 3.21-3.38 (1H, m, C**H**), 3.45 (2H, br s, 2 × C**H**), 6.29 (br s, N**H**), 7.30-7.35 (1H, m, Ar-**H**), 7.60-7.64 (1H, m, Ar-**H**), 8.06 (1H, s, Ar-**H**); LCMS retention time ~1.15, *m/z* 275.1 $[(M+H)^+$, 100%].

Example 41

7-Chloro-1-methyl-exo-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-1,3-dihydro-benzoimidazole-2-thione



(i) ENDO-Methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl ester
Tropenol hydrochloride (15.03g, 0.085mol) and triethylamine (11.9ml, 0.085mol) in $CHCl_3$ (100ml) were cooled to -10°C then methanesulfonyl chloride (6.6ml, 0.085mol) in $CHCl_3$ (50ml) was added dropwise. A second equivalent of MsCl (6.6ml, 0.085mol) was added after 2 hours and a third equivalent (6.6ml, 0.085mol) after 18 hours. The reaction mixture was stirred for 30 minutes after the last addition, then quenched with NH_3/ water (2:1, 300ml) and stirred for another 30 minutes. The solution was diluted with $CHCl_3$, then washed with water (150ml) and brine (150ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the product as a cream solid (13.48g, 80%); δ_H (300MHz, $CDCl_3$); 1.95-1.99 (1H, m, C**H**), 2.25-2.31 (5H, m, NCH_3, 2 × C**H**), 2.33-2.36 (1H, m, C**H**), 2.94 (3H, s, SCH_3), 3.42 (2H, br s, 2 × C**H**), 4.91-4.96 (1H, m, C**H**), 6.06 (2H, s, 2 × C**H**);

(ii) Exo-thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl) ester
To a stirring solution of methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl ester (7.95g, 0.0366mol) in THF/ DMF (100ml, 2% DMF in THF) was added potassium thioacetate (8.37g, 0.0733mol) and the reaction heated to reflux under nitrogen for 24 hours. Silica gel was added and the crude product was concentrated *in vacuo*. The resultant powder was purified by column chromatography (eluent; 5-15% MeOH in DCM). The undesired endo isomer was isolated as a brown oil (1.89g) and the desired thioacetate was obtained as a 3:1 mix of exo:endo isomers (0.670g), which was used without further purification; δ_H (300MHz, $CDCl_3$) 1.62-1.67 (m, C**H**), 1.77-1.81 (4H, m), 2.24-2.28 (m, 4 × CH_3), 2.47-2.57 (2H, m) 3.48 (2H, br s, 2 × C**H**), 3.52 (2H, br s, 2 × C**H**), 3.61-3.73 (1H, m, C**H**), 3.99-4.03 (1H, m, C**H**), 5.99 (2H, s, 2 × C**H**), 6.03 (2H, s, 2 × C**H**).

(iii) [2-Chloro-exo-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-6-nitro-phenyl]-methylamine
(2,3-Dichloro-6-nitro-phenyl)-methylamine (620mg, 2.82mmol) and exo-thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl) ester (670mg, 3.38mmol) in ethanol (20ml) were degassed then NaOH (2.8ml) was added. After stirring for 1 hour the reaction mixture was separated into two portions and crudely purified by elution through an SCX-

2 cartridge. The column was washed with MeOH then the product was eluted with NH_3/ MeOH (~2M) and concentrated *in vacuo*. Purification of this crude material by column chromatography (eluent 0-10% MeOH in DCM) yielded the exo isomer as an orange oil (190mg); δ_H (300MHz, $CDCl_3$); 1.90-1.99 (4H, m, 2 × C**H**$_2$), 2.25 (3H, s, NC**H**$_3$), 3.09-3.12 (3H, m, NHC**H**$_3$), 3.40-3.58 (3H, m, C**H**, 2 × C**H**), 6.01 (2H, s, 2 × C**H**), 6.55-6.61 (1H, m, Ar-**H**), 7.08 (1H, br s, N**H**), 7.88-7.92 (1H, m, Ar-**H**) and the endo isomer as an orange oil (170mg).

(iv) 3-Chloro-N^2-methyl-exo-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-benzene-1,2-diamine

[2-Chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-6-nitro-phenyl]-methyl-amine (190mg, 0.560mmol) and $SnCl_2 \cdot 2H_2O$ (630mg, 2.80mmol) were heated to between 60-70°C; the colour of the reaction changed from orange to darker orange. Stirring was continued for 2 hours then the solution was filtered to remove a yellow precipitate, washed with $NaHCO_3$ (50ml) and extracted with ethyl acetate (3 × 50ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude diamine as an orange oil (86mg, 50%) which was used without further purification; δ_H (300MHz, $CDCl_3$); 1.62-1.74 (4H, m, 2 × C**H**$_2$), 2.15 (3H, s, NC**H**$_3$), 2.61 (3H, s, NHC**H**$_3$), 2.92-3.06 (1H, m, C**H**), 3.38 (2H, br s, 2 × C**H**), 5.81 (2H, s, 2 × C**H**), 6.46-6.48 (1H, m, Ar-**H**), 7.00-7.05 (1H, m, Ar-H); LCMS retention time ~1.12min, *m/z* 310.1 $[(M+H)^+$, 58%]

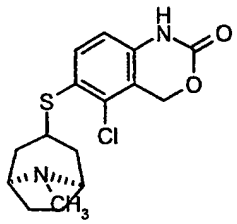
(v) 7-Chloro-1-methyl-exo-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-1,3-dihydro-benzoimidazole-2-thione

3-Chloro-N^2-methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-benzene-1,2-diamine (86mg, 0.278mmol) and triethylamine (0.155ml, 1.11mmol) in THF (3ml) were cooled to 0°C and thiophosgene (0.023ml, 0.306mmol) was added. Stirred for 1 hour at 0°C then the mixture was concentrated *in vacuo*. Purification by mass-guided preparative LCMS furnished the acetic acid salt of the product in solution. This was converted to the free base by application of this aqueous solution to an SCX-2 cartridge, washing with MeOH then elution of the product with NH_3/ MeOH (~2M). The ammoniacal solution

was concentrated *in vacuo* to yield the title compound as a yellow solid (42mg, 43%); δ_H (300MHz, $CDCl_3$); 1.91-2.00 (2H, m, 2 × CH), 2.10 (3H, s, NCH_3), 2.19-2.31 (2H, m, 2 × CH), 3.01-3.15 (1H, m, CH), 3.80 (2H, br s, 2 × CH), 6.02 (2H, s, 2 × CH), 6.48-6.50 (1H, m, Ar-H), 7.28-7.31 (1H, m, Ar-H); LCMS retention time ~1.78 min, *m/z* 352.1 $[(M+H)^+]$.

Example 42

5-Chloro-6-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]-1,4-dihydro-2H-3,1-benzoxazin-2-one



(i) Methyl-2,3-dichloro-6-nitrobenzoate

To a stirred solution of methyl-2,3-dichlorobenzoate (10g, 48.7mmol) in concentrated sulphuric acid (40ml), cooled to 5^0C, was added dropwise, (at such a rate to keep the reaction temperature < 25^0C), concentrated nitric acid (8.4ml, 82.9mmol). The mixture was then stirred at ambient temperature for 2h.

The mixture was poured slowly into water (200ml) and stirred for 2h. The suspension was filtered, the filter cake washed with more water on the sinter, and dried *in vacuo* to give the crude product as a white solid (10.3g). The crude product was recrystallised from hexane, the crystallised solid (5-nitro isomer) removed by filtration, and the mother liquors evaporated *in vacuo*. The resultant white solid was recrystallised from hexane and the crystallised solid collected by filtration and dried *in vacuo* to give the product as a white crystalline solid (1.3g).

(ii) Methyl-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]-6-nitrobenzoate

To a stirred solution of methyl-2,3-dichloro-6-nitrobenzoate (3.6g, 14.4mmol) in ethanol (75ml) was added a solution of ENDO-methanesulfonic acid 8-methyl-8-aza-

bicyclo[3.2.1]oct-3-yl ester (4.3g, 21.6mmol) in ethanol (75ml) and then 2M sodium hydroxide (10.8ml, 21.6mmol). The mixture was stirred under nitrogen at ambient temperature for 24h. The mixture was evaporated *in vacuo* to give a viscous orange oil (10.7g).

The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2 5% MeOH 0.1% NH_4OH) to give the product as a yellow solid (3.0g).

(iii) Methyl-6-amino-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]benzoate

To a stirred solution of methyl-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]-6-nitrobenzoate (3.0g, 8.1mmol) in ethyl acetate (400ml) was added tin chloride dihydrate (9.14g, 40.5mmol) and the mixture was heated under reflux for 2h.
The mixture was allowed to cool and then poured into saturated sodium bicarbonate (400ml). The organic phase was separated and the aqueous phase extracted 2x with ethyl acetate. The combined organic phases were washed with (1) water and (2) saturated sodium chloride solution, dried ($MgSO_4$) and evaporated *in vacuo* to give a brown viscous oil (2.2g). The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2 20% MeOH 0.1% NH_4OH) to give the product as a light-brown oil (1.76g).

(iv) {6-Amino-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]phenyl}methanol

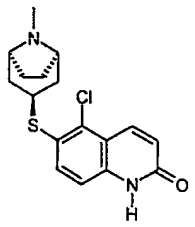
To a suspension of lithium aluminium hydride (180mg, 4.7mmol) in dry tetrahydrofuran (5ml) was added a solution of methyl-6-amino-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]benzoate (800mg, 2.35mmol) in tetrahydrofuran (20ml) and the mixture stirred at ambient temperature for 4h.
The mixture was quenched with water, filtered and the filter cake washed with ethanol. The combined filtrate and washings were evaporated *in vacuo* to give a yellow gum (774mg). The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2 20% MeOH 0.1% NH_4OH) to give the product as a light-yellow oil (408mg).

(v) 5-Chloro-6-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]-1,4-dihydro-2H-3,1-benzoxazin-2-one

To a solution of {6-Amino-2-chloro-3-[endo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)thio]phenyl}methanol (372mg, 1.2mmol) and triethylamine (0.83ml, 5.96mmol) in chloroform (10ml), cooled to -10^{0}C, was added, dropwise, a 20% solution of phosgene in toluene (0.66ml, 1.3mmol). The mixture was allowed to warm to ambient temperature and stirred for 2h. The mixture was evaporated *in vacuo* to give an orange solid (1.24g). The crude product was purified by ion-exchange chromatography (SCX 500mg pre-washed with methanol; washed with methanol and eluted with 2M methanolic ammonia); evaporation *in vacuo* gave a yellow oil (228mg). Further purification by preparative mass-guide LC-MS gave the acetate of the product as a yellow oil (230mg). Final purification by ion-exchange chromatography as above gave the free base of the title compound as a white foam (148mg, 37%). ^{1}H NMR (300MHz; CD_3OD): 1.5-1.6 (2H, m, CH_2), 1.63-1.72 (4H, m, 2x CH_2),1.9- 2.0 (2H, m, CH_2), 2.2 (3H, s, NCH_3), 3.2-3.35 (3H, m, 3x CH), 4.65 (2H, s, O-CH_2), 6.65 (1H, d, Ar-H), 7.35 (1H, d, Ar-H). LC-MS retention time ~ 1.4min, m/z (FIAPOSES) 339.1 [M+H+, 100%].

Example 43

EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one



(i) 6-Chloro-5-nitroquinoline

A solution of 6-chloroquinioline (5g, 30.6mmol) in 30mL cH_2SO_4 was cooled to 0°C. Sodium nitrite (70mg, 1mmol) was added followed by $cHNO_3$ (2.5mL) dropwise at a rate to keep the temperature between 0°C and 10°C. The mixture was stirred at 0°C for 45 mins and at room temperature for 1 hour. After this time, the mixture was poured into ice and c NH_3 solution added until pH = 7 (with cooling). The mixture was then filtered and the residue dried *in vacuo* to give 6-Chloro-5-nitroquinoline as an off-white solid (5.7g, 89%); H (300MHz; $CDCl_3$) 7.85 (1H, dd), 8.05 (1H, d), 8.25 (1H, d), 8.35 (1H, d) and 9.10 (1H, d).

(ii) 6-Chloro-5-nitroquinoline -N-oxide

m-Chloroperbenzoic acid (70-75% by wt, 2.7g, 15.6mmol) was added in portions to a stirred , ambient temperature solution of 6-chloro-5-nitroquinoline (2g, 9.6mmol) in $CHCl_3$ (15mL). The mixture was stirred for 6h. After this time, more $CHCl_3$ was added, followed by 30mL of a saturated aqueous solution of Na_2CO_3 and 1mL 1M NaOH. The mixture was separated and the aqueous phase extracted with $CHCl_3$ (x2). The organic phases were combined and washed with a saturated aqueous solution of Na_2CO_3, H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give 6-Chloro-5-nitroquinoline -N-oxide as a yellow solid (1.8g, 84%); H (300MHz; $CDCl_3$) 7.6 (1H, m), 7.7 (1H, d), 7.95 (1H, d), 8.65 (1H, d) and 8.75 (1H, d).

(iii) EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-5-nitro-quinoline-N-oxide

A mixture of 6-chloro-5-nitroquinoline-N-oxide (2.68g, 11.7mmol) and exo-thioacetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (3g, 15.1mmol) in de-gassed MeOH (120mL) was treated with 15mL of 2M NaOH and stirred at room temperature under an atmosphere of nitrogen for 48h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography using an ISCO CombiFlash system (2x120g column, eluent 40-50% MeOH (containing 1% NH_3) in CH_2Cl_2). The title compound was obtained as a yellow-brown semi-solid (90-95% pure) (2.1g, 52%); H (300MHz; $CDCl_3$) 1.9 (2H, m), 2.1 (2H, m), 2.3 (2H, m), 2.69 (2H, m), 3.3 (3H, s), 3.81 (2H, m), 3.99 (1H, m), 7.70 (1H, t), 7.8 (1H, d), 8.2 (1H, d), 8.7 (1H, d) and 8.8 (1H, d).

(iv) EXO-5-Amino-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-quinoline-N-oxide

A mixture of EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-5-nitro-quinoline-N-oxide (1.9g, 5.5mmol) and tin (II) chloride dihydrate (7g, 27.5mmol) in EtOAc (200mL) was heated under reflux for 18h. The hot solution was filtered and the organic phase carefully washed with 33% aq NH_3. The residue was washed with 33% aq NH_3 and the aqueous phase extracted with EtOAc. The organic phases were then combined, dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give the title compound as a bright yellow foam (550mg, 32%); H (300MHz; $CDCl_3$) 1.49 (2H, m), 1.70 (2H, m), 1.85 (2H,

m), 1.97 (2H, m), 2.24 (3H, s), 3.15 (3H, m), 5.27 (2H, bs), 7.22 (1H, t), 7.72 (2H, t), 8.04 (1H, d) and 8.48 (1H, d).

(v) EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-quinoline-N-oxide

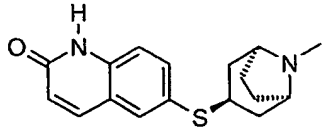
To a stirred solution of EXO-5-Amino-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-quinoline-N-oxide (500mg, 1.6mmol) in cHCl (4mL) in H_2O (2mL) cooled to –5°C was added a solution of sodium nitrite (110mg, 1.6mmol) in H_2O (0.6mL). After stirring at low temperature for 15 mins, the mixture was added to a stirred suspension of copper (I) chloride (630mg, 6.3mmol) in cHCl (1.3mL) heated to 83-65°C. The combined mixture was stirred at elevated temperature for 5 mins. Ice was added and the mixture made alkaline with 10% NaOH, extracted with $CHCl_3$ (x5), washed with brine and the organic phase dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting residue purified by flash column chromatography using the ISCO CombiFlash system (35g column, eluent 15-30% MeOH (containing 1% NH_3) in CH_2Cl_2) to give the title compound as a colourless solid (98mg, 18%); H (300MHz; $CDCl_3$) 1.65 (2H, m), 1.90 (4H, m), 2.12 (2H, m), 2.34 (3H, s), 3.20 (2H, m), 3.65 (1H, m), 7.35 (1H, t), 7.65 (1H, d), 8.05 (1H, d), 8.45 (1H, d) and 8.65 (1H, d).

(vi) EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one

Benzoyl chloride (45mg, 0.32mmol) was added dropwise to a vigorously stirred two-phase mixture of EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-quinoline-N-oxide (90mg, 0.27mmol) and NaOH (25mg, 0.62mmol) in H_2O (0.8mL) and CH_2Cl_2 (0.42mL). The reaction mixture was allowed to stir at room temperature for 1h and then filtered. The residue was washed with CH_2Cl_2 and H_2O and dried *in vacuo*. The solid was purified by LC-MS to give the acetate salt of the title compoundas a colourless solid (11.3mg, 11%); H (300MHz; $CDCl_3$) 2.05 (6H, m), 2.29 (2H, m), 2.65 (3H, s), 3.65 (1H, m), 3.75 (2H, m), 6.75 (1H, d), 7.35 (1H, d), 7.75 (1H, d) and 8.35 (1H, d).

Example 44

EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one



(i) 2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride

To an ice bath cooled stirred slurry of 2-hydroxyquinoline (30.5g, 0.210mol) in dichloromethane (300cm^3) was added chlorosulphonic acid (70cm^3, 1.05mol) in 4 equal sized batches. This was left to stir at room temperature for 2 days then slowly poured onto crushed ice. Large amount of a white solid formed in the lower chlorinated layer. This was filtered off and dried *in vacua* to yield 2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride as a dry white solid (36.3g); δ_H (300MHz; D6 DMSO) 6.51-6.59 (1H, m, 1 x Ar-**H**), 7.29-7.34 (1H, m, Ar-**H**), 7.71-7.79 (1H, m, Ar-**H**), 7.90-7.96 (1H, m, Ar-**H**) and 8.00-8.06 (1H, m, Ar-**H**); LCMS retention time ~ 3.43min, m/z (FIANEG) 241.9 [$Cl^{35}(M)^-$, 100%] and 244.0 [$Cl^{37}(M)^-$, 33%]. NMR and LCMS showed that this material contained some starting material as a minor impurity but no further purification was performed.

(ii) Thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester

To an ice bath cooled, stirred mixture of impure 2-Oxo-1,2-dihydro-quinoline-6-sulfonyl chloride (20g, ~82mmol), acetic acid (240cm^3) and acetic anhydride (80cm^3) was added sodium acetate (24g) in three equal sized batches. Then Zinc (20g) was added in small batches (exothermic reaction). After one hour the ice bath was removed and the reaction was left stirring at room temperature for five days then concentrated *in vacuo* then triturated with water (~200cm^3). The solid that was formed was filtered off and dried *in vacua* to yield Thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester as a dry grey solid (11.7g, ~65%); δ_H (300MHz; D6 DMSO) 2.42 (3H, s, $COCH_3$), 6.51-6.57 (1H, m, Ar-**H**), 7.32-7.37 (1H, m, Ar-**H**), 7.43-7.48 (1H, m, Ar-**H**), 7.72 (1H, s, Ar-**H**), 7.88-7.92 (1H, m, Ar-**H**) and 11.95 (1H, br s, N-**H**); LCMS retention time ~ 3.03min, m/z (FIAPOS) 220 [$(M+H)^+$, 100%].

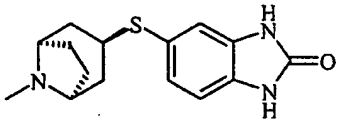
(iii) EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one

To a stirred mixture of thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester (3.00g, 13.7mmol) and ENDO-methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (2.7g, 12.3mmol) with 2-propanol (~150cm^3) was added pyrrolidine (1.14cm^3, 13.7mmol) in one quick injection, at room temperature, under a flow of nitrogen gas causing a strong

yellow colouration. The reaction was then treated with potassium carbonate (2.1g, 15.2mmol) and then heated to 80°C. The reaction was maintained at this temperature overnight then cooled to room temperature and concentrated *in vacuo* to a yellow paste. This was treated with 1N HCl ($100cm^3$) and washed with $CHCl_3$ ($3x50cm^3$). The aqueous layer was filtered through paper and then basified using 2N NaOH (~$50cm^3$), then extracted with $CHCl_3$ ($3x50cm^3$). The organics were dried ($MgSO_4$) and concentrated *in vacuo* then columned on silica (gradient elution, 98:2 to 85:15, CH_2Cl_2:methanolic ammonia) but NMR still showed some minor impurities. The solid was recrystallised by dissolving in the minimum warm (~50°C) EtOAc and methanol (1:1, ~$10cm^3$), then slowly cooling to room temperature, thus yielding EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one (213mg) as fine colourless crystals; δ_H (300MHz; $CDCl_3$) 1.50-1.60 (2H, m, 2 x one of CH_2), 1.70- 1.87 (4H, m, 4 x one of CH_2), 1.98-2.06 (2H, m, 2 x one of CH_2), 2.21 (3H, s, NCH_3), 3.10-3.27 (3H, m, HCS and 2 x NCH), 6.62-6.70 (1H, m, Ar-H), 7.20-7.27 (1H, m, Ar-H), 7.50-7.56 (1H, m, Ar-H), 7.62-7.64 (1H, m, Ar-H) and 7.70-7.73 (1H, m, Ar-H); LCMS retention time ~ 2.03 min, m/z (FIAPOSES) 301.1 $[(M+H)^+$, 100%].

Example 45

Exo-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one

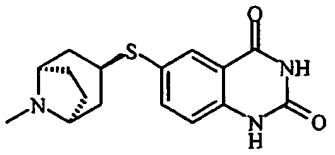


By proceeding in a similar manner to Example 44 but using 1,3-dihydro-2H-benzimidazol-2-one in place of 2-hydroxyquinoline there was prepared the title compound as colourless solid. m.p. = 178.5-181.6°C.

^1H nmr; δ_H (300MHz; C_2D_6SO) 1.42-1.5 (2H, m, CH_2), 1.60-1.65 (4H, 2 x CH_2), 1.72-1.82 (2H, m, CH_2), 2.08-2.14 (3H, s, NCH_3), 3.00-3.05 (2H, m, $NCHCH_2$), 3.10-3.23 (1H, m, HCS), 6.87-6.89 (1H, m, Ar-H), 6.95-6.97 (1H, s, Ar-H), 7.00-7.04 (1H, m, Ar-H), 10.60-10.68 (1H, s, NH), 10.72-10.82 (1H, s, NH); LCMS retention time ~0.803 min, m/z (FIAPOSES) 290.1 $[(M+H)^+$, 97.8%].

Example 46

Exo-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-2,4-(1H,3H)-quinazolindione

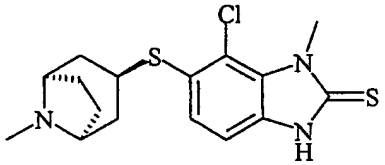


By proceeding in a similar manner to Example 44 but using 2,4-(1H,3H)-quinazolindione in place of 2-hydroxyquinoline there was prepared the title compound as colourless solid. m.p. >260°C

^{1}H nmr, δ_H (300MHz; C_2D_6SO) 1.60-1.78 (6H, m, 3 x CH_2), 1.92-2.05 (2H, m, CH_2), 2.25-2.30 (3H, s, NCH_3), 3.28-3.48 (1H, m, HCS; 2H, m, $NCHCH_2$), 7.10-7.15 (1H, m, Ar-H), 7.65-7.72 (1H, m, Ar-H), 7.83-7.88 (1H, s, Ar-H), 8.24-8.35 (1H, s, HCOOH), 10.90-11.90 (2H, s, 2 x NH); LCMS retention time ~0.910 min, m/z (FIAPOSES) 318.1 $[(M+H)^+, 97.4\%]$.

Example 47

Exo-7-chloro-1-methyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazole-2-thione



(i) 2,3-dichloro-N-methyl-6-nitroaniline

2,3-dichloro-6-nitroaniline (1.026g, 5mmole), was suspended in toluene (10ml). To this vigorously stirred suspension was added 50% aqueous sodium hydroxide solution (1.7g), tertiary-butyl ammonium chloride (0.07g, 0.25mmole) and dimethyl sulfate (0.51ml, 5.4mmole). After 4hr stirring at room temperature the intense red solution was washed with water, brine, dried with magnesium sulfate, filtered, evaporated *in vacuo*. Weight = 1.03g, m.p. = 82°C.

Spectra: ^{1}H nmr, δ_H (300MHz; $CDCl_3$) 2.96-3.05 (3H, d, N-CH_3), 6.60-6.65 (1H, d, Ar-H; 1H, m, N-H), 7.72-7.80 (1H, d, Ar-H); LCMS retention time ~5.959 min, m/z (GRADNL.M) = 219.1 [$(M-H)^-$, 100%].

(ii) Exo-2-chloro-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-6-nitroaniline

2,3-dichloro-N-methyl-6-nitroaniline (3.99g, 18mmole) and (8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethanethioate (4.92g, 24.7mmole) were stirred in ethanol (90ml). To this was added 2M aqueous sodium hydroxide (25ml, 50mmole). The solution was stirred magnetically, at room temperature, for 24 hr, under a nitrogen atmosphere. The mixture was evaporated *in vacuo*, dissolved in chloroform, washed with water, then brine. The chloroform solution was extracted with 5M HCl, this was washed with chloroform. The acid extract was basified with aqueous 50% sodium hydroxide, and extracted into chloroform, washed with brine, dried with magnesium sulfate, filtered, evaporated in vacuo, purified by flash chromatography, using 1% ammonia-methanol: dichloromethane (0% to 10%). Weight = 0.512g of red oil, that crystallised on standing, m.p. = 89°C.

Spectra: ^{1}H nmr, δ_H (300MHz; $CDCl_3$) 1.64-1.72 (2H, m, CH_2), 1.83-1.93 (4H, m, 2 x CH_2), 2.08-2.14 (2H, m, CH_2), 2.30-2.34(3H, s, NCH_3), 3.11-3.14 (3H, d, NCH_3) 3.21-3.24 (2H, m, $NCHCH_2$), 3.50-3.62 (1H, m, HCS), 6.62-6.65 (1H, d, Ar-H), 7.00-7.10 (1H, s, N-H), 7.90-7.92 (1H, d, Ar-H), LCMS retention time ~1.930 min, m/z (GRADNL.M) = 342.1 [$(M-H)^+$, 100%]

(iii) Exo-3-chloro-N^2-methyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-benzenediamine

Exo-2-chloro-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-6-nitroaniline (0.512g, 1.5mmole) was dissolved in ethyl acetate (20ml), and to this was added $SnCl_4.2H_2O$ (1.69g, 7.5mmole). The stirred mixture was brought to reflux, under a nitrogen atmosphere, and held at this temperature for 20 min. The supernatent liquid of the cooled solution was added to an acid ion-exchange solid phase contained in a cartridge (10g, SCX-2). A gum that remained in the flask was repeatedly extracted into ethyl acetate, and this was also added to the cartridge. The cartridge was washed with

ethyl acetate, then methanol. The product was stripped off the cartridge using 2M NH_3 in methanol. The fractions containing product were combined, re-filtered to remove residual tin residues, evaporated *in vacuo*. Weight of solid (broad m.p.), = 0.471g. Spectra: ^1H nmr, δ_H (300MHz; CD_3OD) 1.92-2.95 (6H, m, 3 x CH_2), 2.22-2.34 (2H, m, CH_2), 2.65-2.70 (3H, s, NCH_3), 2.75-2.77 (3H, broad singlet, NCH_3), 3.34-3.50 (1H, m, HCS), 3.85-3.92 (2H, m, $NCHCH_2$), 6.64-6.70 (1H, d, Ar-H), 7.12-7.15 (1H, d, Ar-H), LCMS retention time ~1.223 min, m/z (GRADNL.M) = 312.1 $[(M-H)^+$, 100%]. Similarly prepared were: Exo-3-chloro-N^2-propyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-benzenediamine (an oil), m/z (GRADNL.M) = 340.1, and Exo-3-chloro-N^2-isopropyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-benzenediamine (an oil),), m/z (GRADNL.M) = 340.1

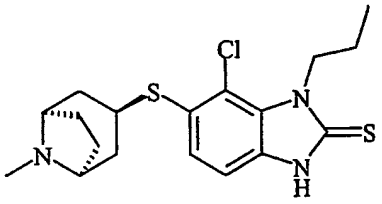
(iv) Exo-7-chloro-1-methyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazole-2-thione

Exo-3-chloro-N^2-methyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-benzenediamine (0.475g, 1.52 mmole) was dissolved in THF (15 ml) and DMF (15ml). Triethylamine (0.86ml, 6.16mmole) was added and the solution was cooled to 0°C in an ice-water bath. Thiophosgene (0.134ml, 1.76mmole) was dissolved in THF (10ml) and added, with stirring, dropwise, to the solution of the benzendiamine, at such a rate that the temperature did not exceed 10°C. On completion of addition the mixture was stirred at ambient temperature for 1hr. The mixture was evaporated *in vacuo*, the residue was dissolved in water, if necessary using a few drops of acetic acid to aid solubilisation. This solution was added to an acid ion-exchange resin contained in a cartridge (10g, SCX-2), the cartridge was washed through with water, then methanol. The product could be stripped off using 2M-NH_3 in methanol. Fractions containing product were bulked, evaporated, and purified by flash chromatography using florisil as stationary phase and gradient elution with methanol: chloroform (2% to 10%). Weight = 0.0494g, m.p. = 217.3-219.1°C.

Spectra: ^1H nmr, δ_H (300MHz; $CDCl_3$) 1.70-1.88 (2H, m, CH_2), 1.92-1.98 (2H, m, CH_2), 2.06-2.35 (4H, m, 2 x CH_2; 3H, s, NCH_3), 3.10-3.24 (1H, m, HCS), 3.45-3.52 (2H, m, $NCHCH_2$), 4.10-4.14 (3H, s, NCH_3), 6.50-6.52 (1H, s, Ar-H), 7.22-7.25 (1H, s, Ar-H), LCMS retention time ~2.603 min, m/z (FIAPOSES) = 354.1 $[(M+H)^+$, 98.6%].

Example 48

Exo-7-chloro-1-propyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazole-2-thione

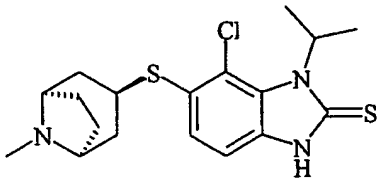


By proceeding in a similar manner to Example 47 there was prepared the title compound as colourless solid. m.p. = 131.4-133.9°C.

^{1}H nmr, δ_H (300MHz; $CDCl_3$) 1.00-1.06 (3H, m, CH_3), 1.08-1.22 (2H, m, CH_2), 1.70-2.12 (8H, m, 4 x CH_2), 2.20-2.22 (3H, s, NCH_3), 3.14-3.25 (1H, m, HCS), 3.38-3.42 (2H, m, $NCHCH_2$), 4.52-4,58 (2H, m, CH_2), 6.70-6.72 (1H, s, Ar-H), 7.25-7.30 (1H, s, N-H; 1H, s, Ar-H), LCMS retention time ~2.291 min, m/z (FIAPOSES) 382.1 [$(M+H)^+$, 100%]

Example 49

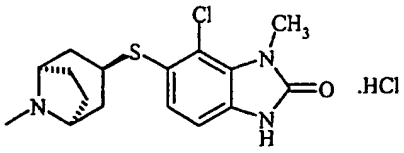
Exo-7-chloro-1-isopropyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazole-2-thione



By proceeding in a similar manner to Example 47 there was prepared the title compound as colourless solid. m.p. = 228.9-230.9°C. Spectra: ^{1}H nmr, δ_H (300MHz; $CDCl_3$) 1.58-1.60 (6H, d, 2 x CH_3), 1.72-2.08 (8H, m, 4 x CH_2), 2.28-2.30 (3H, s, NCH_3), 3.23-3.40 (2H, m, $NCHCH_2H$; 1H, m, HCS), 5.48-5.60 (1H, m, C-H), 7.17-7.19 (1H, s, Ar-H), 7.42-7.48(1H, s, Ar-H), LCMS retention time ~2.115 min, m/z (FIAPOSES) = 382.1 [$(M+H)^+$, 98.2%]

Example 50

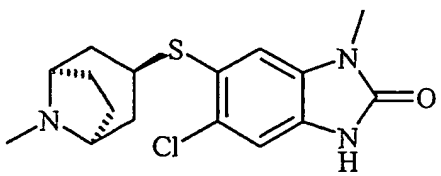
Exo-7-chloro-1-methyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one hydrochloride



Exo-3-chloro-N^2-methyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-benzenediamine [Example 46 (iii), 0.471g, 1.51mmole], was dissolved in a mixture of THF (20ml) and DMF (20ml). To this was added triethylamine (0.86ml, 6.16mmole), and the mixture was cooled to 0°C in an ice-water bath. A 20% phosgene in toluene solution was added, dropwise, to this stirred solution, at a rate that the temperature never exceeded 10°C. The solution was allowed to stir at ambient temperature for 1hr, the mixture was then evaporated *in vacuo*. The residue was dissolved in water (a few drops of acetic acid were added to facilitate solubilisation), and added to an acid ion-exchange polymer in a cartridge (10g, SCX-2). The cartridge was washed with water, then methanol, the product was stripped off using 2M NH_3 in methanol. Fractions containing product were bulked, evaporated, purified by flash chromatography, gradient elution using ammonia-methanol:dichloromethane (0% to 12.5%). Fractions containing product were bulked, dissolved in chloroform, and enough ethereal HCl was added such that the solution was acid by pH paper. The solution was evaporated to dryness, triturated with dry ether, filtered, dried. Weight = 0.0879g, m.p. >260°C. . Spectra: ^{1}H nmr, □H (300MHz; CD_3OD) 1.95-2.40 (8H, m, 4 x CH_3), 2.70-2.80 (3H, s, NCH_3), 3.42-3.55 (1H, m, HCS), 3.72-3.75 (3H, s, NCH_3), 3.86-3.92 (2H, m, $NCHCH_2H$) 6.99-7.20 (1H, s, Ar-H), 7.36-7.42 (1H, s, Ar-H), LCMS retention time ~1.468 min, m/z (FIAPOSES) = 338.1 [$(M+H)^+$, 100%]

Example 51

Exo-5-chloro-1-methyl-6-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-1,3-dihydro-2H-benzimidazol-2-one

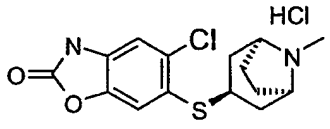


By proceeding in a similar manner to examples 47 and 50 but using 3,4-dichloro-N-methyl-6-nitroaniline there was prepared the title compound as a colourless solid. m.p. = 206.4-207.2°C

^{1}H nmr, δ_H (300MHz; $CDCl_3$) 1.63-1.73 (2H, m, CH_2), 1.90-1.96 (4H, 2 x CH_2), 2.04-2.10 (2H, m, CH_2), 2.10-2.14 (3H, s, NCH_3), 3.11-3.20 (1H, m, HCS), 3.12-3.25 (2H, m, $NCHCH_2$), 3.25-3.35 (3H, s, NCH_3), 6.75-6.78 (1H, s, Ar-H), 7.05-7.08 (1H, s, Ar-H), 12.05-12.95 (1H, s, NH); LCMS retention time ~1.966 min, m/z (FIAPOSES) 338.1 [$(M+H)^+$, 100%].

Example 52

EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt



(i) 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonic acid

To a stirred mixture of chlorzoxazone (10g, 58.9mmol) and CH_2Cl_2 (~500cm^3) was added chlorosulphonic acid (4.3cm^3, 64.8mmol) at room temperature. The reaction was left at room temperature for a week whereupon all the solvent had evaporated leaving a white solid. NMR showed a 1:2 mixture of product and starting material respectively. This crude was extracted with H_2O (3 x 15cm^3), then the aqueous was concentrated *in vacuo* to a sticky solid which was washed with CH_2Cl_2 (4 x 40cm^3) to yield 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonic acid as a fine white solid; δ_H (300MHz; D6 DMSO) 7.10 (1H, s, Ar-**H**), 7.68 (1H, s, Ar-**H**) and 11.80 (1H, s, N-**H**); LCMS retention time ~ 0.47min, m/z (FIANEG) 247.9 [Cl^{35} $(M-H)^-$, 100%] and 249.9 [Cl^{37} $(M-H)^-$, 33%].

(ii) 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonyl chloride

To a stirred mixture of 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonic acid (~10g, 40mmol) and CH_2Cl_2 was added thionyl chloride (5.8cm^3, 80mmol) at room temperature, causing gas to be evolved. This was stirred at room temperature for two hours but the

solid didn't dissolve and FIA only showed starting material. Therefore a few drops of DMF were added and the reaction heated to 50°C overnight but no reaction occurred. The starting material was filtered off and then treated with neat thionyl chloride (15cm^3) and heated to 70°C overnight, FIA now detected starting material and product, so the reaction was treated with DMF (2 x 1cm^3) to aid solvation, FIA showed completion of the reaction. The reaction was diluted with CH_2Cl_2 (100cm^3) then poured onto ice. The solid formed was filtered off and dried *in vacuo* yielding 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonyl chloride (4.6g, 43%) as a fine white solid; δ_H (300MHz; D6 DMSO) 7.09 (1H, s, Ar-**H**), 7.69 (1H, s, Ar-**H**) and 11.81 (1H, s, N-**H**); m/z (FIANEG) 266.0 [(M-H)$^-$, 100%] and 268.0 [(M-H)$^-$, 67%].

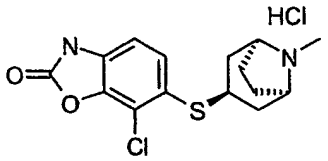
(iii) Thioacetic acid *S*-(3-acetyl-5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl) ester
To an ice bath cooled stirred solution of 5-Chloro-2-oxo-2,3-dihydro-benzooxazole-6-sulfonyl chloride (4.6g, 17.2mmol) in acetic acid (60cm^3) and acetic anhydride (20cm^3) was added sodium acetate (8g). This mixture was treated with zinc (5 x 1g) in batches due to the strongly exothermic reaction. This was stirred at room temperature overnight to give a pale grey slurry. The reaction was concentrated *in vacuo* then treated with H_2O. The solid was filtered off and washed with more H_2O then dried *in vacuo* to yield thioacetic acid *S*-(3-acetyl-5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl) ester as a a grey solid (4.4g, 90%); δ_H (300MHz; D6 DMSO) 2.48 (3H, s, $COCH_3$), 2.60 (3H, s, $COCH_3$), 7.72 (1H, s, Ar-**H**) and 8.08 (1H, s, Ar-**H**); LCMS retention time ~4.86min.

(iv) EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt
To a stirred mixture of thioacetic acid *S*-(3-acetyl-5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl) ester (2.00g, 6.98mmol), ENDO-methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (1.53g, 6.98mmol) and cesium fluoride (1.05g, 6.98mmol) in DMF was added pyrrolidine (1.17cm^3, 14.0mmol) in one quick injection, at 80°C, under a flow of nitrogen gas. The reaction was maintained at this temperature overnight then treated with acetic anhydride (1cm^3) and concentrated *in vacuo* to a sticky oil. This was purified using SCX powder to yield a thick brown oil which was triturated with CH_2Cl_2 and diethyl ether to yield a very insoluble powder. This powder was stirred for two days

in 0.5N $HCl_{(aq)}$ and then treated with methanol. Not all of the solid would dissolve so the mother liquor was filtered and concentrated *in vacuo* to yield EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt (48mg) as a pale yellow solid; δ_H (300MHz; D4 methanol) 1.81-2.27 (8H, m, 4 x CH_2), 2.62 (3H, s, NCH_3), 3.41-3.59 (1H, m, HCS), 3.75-3.85 (2H, m, 2 x NCH), 7.25 (1H, s, Ar-H) and 7.43 (1H, s, Ar-H); LCMS retention time ~ 2.10 min, m/z (FIAPOSES) 325.0 [Cl^{35} $(M+H)^+$, 100%] and 327.0 [Cl^{37} $(M+H)^+$, 33%].

Example 53

EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt



(i) 2-Chloro-3-fluoro-6-nitro-phenol

2-Chloro-3-fluoro-6-nitro-phenol (3g, 15.7mmol) was prepared using a literature procedure from 2-Chloro-1,3-difluoro-4-nitro-benzene. (Hayakawa, Isao; Hiramitsu, Tokiyuki; Tanaka, Yoshiaki; Chem.Pharm.Bull.; 32; *12*; **1984**; 4907-4913);

(ii) EXO-2-Chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-6-nitro-phenol

To a stirred solution of 2-Chloro-3-difluoro-6-nitro-phenol (3g, 15.7mmol) and EXO-Thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl) ester (4.8g, 24.1mmol) in ethanol (100cm^3) was added 2N NaOH (2 x 12cm^3) at room temperature under a flow of nitrogen gas. The reaction was stirred at room temperature overnight then concentrated *in vacuo,* diluted with H_2O (50cm^3) then treated with 2N HCl causing rapid formation of solid. This solid was washed with 2N $HCl_{(aq)}$, $CHCl_3$ and methanol to yield EXO-2-Chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-6-nitro-phenol (966mg, 19%) as a fine yellow solid; δ_H (300MHz; D6 DMSO) 2.09-2.34 (8H, m, 4 x CH_2), 2.50 (3H, s, NCH_3), 3.80-4.03 (3H, m, SCH and 2 x NCH), 7.15-7.29 (1H, m, Ar-H) and 7.88-7.99 (1H, m, Ar-H); LCMC retention ~2.75min, m/z (FIAPOS) 329.1 [Cl^{35} $(M+H)^+$, 100%] and 331.0 [Cl^{37} $(M+H)^+$, 33%].

(iii) EXO-6-Amino-2-chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol hydrochloride salt

A slurry of EXO-2-Chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-6-nitro-phenol (1.67g, 5.1mmol) in methanol was treated with ethanolic HCl and then water to try to aid solvation but solid still remained. His mixture was added to a cooled slurry of 5% Pd/C (400mg) with ethanol. This mixture was placed under a pressurised atmosphere of hydrogen gas (60 PSI) at room temperature for one hour. The organic solid had dissolved leaving the undissolved palladium on charcoal. The reaction was filtered through celite® then concentrated *in vacuo* to yield EXO-6-Amino-2-chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol hydrochloride salt (1.55g, 91%) as a white crystalline solid; δ_H (300MHz; D4 methanol) 2.10-2.51 (8H, m, 4 x CH_2), 2.79 (3H, s, NCH_3), 3.79-3.92 (1H, m, SC**H**), 4.02-4.10 (2H,m, 2 x NC**H**), 7.25-7.32 (1H, m, Ar-**H**) and 7.37-7.43 (1H, m, Ar-**H**); LCMC retention ~0.92min, m/z (FIAPOS) 150.1 [Cl^{35} $(M+2H)^{2+}$, 90%], 151.1 [Cl^{37} $(M+2H)^{2+}$, 30%], 299.1 [Cl^{35} $(M+H)^{+}$, 100%] and 301.1 [Cl^{37} $(M+H)^{+}$, 33%].

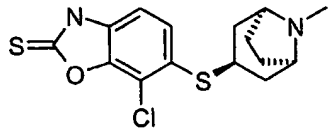
(iv) EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt

To a stirred solution EXO-6-Amino-2-chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol hydrochloride salt (506mg, 1.7mmol) and triethylamine (684mg, 6.8mmol) in $CHCl_3$ (30cm^3) was added a solution of triphosgene (167mg, 0.56mmol) as a solution in $CHCl_3$ (3 x 2cm^3) causing an exothermic reaction. The reaction was concentrated *in vacuo* to a greyish brown solid which was washed with methanol (3 x 10cm^3) to yield a brown solution and a sticky grey paste. The solid was dried *in vacuo* overnight then dissolved in a mixture of methanol (100cm^3) and $CHCl_3$ (5cm^3) and treated with a few drops of ethanolic HCl solution. This solution was concentrated *in vacuo* to yield EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one hydrochloride salt (160mg) as a fluffy white solid; δ_H (300MHz; D4 methanol) 1.82-2.26 (8H, m, 4 x CH_2), 2.65 (3H, s, NCH_3), 3.35-3.49 (1H, m, **H**CS), 3.72-3.83 (2H, m, 2 x NC**H**), 6.90-7.01 (1H, m, Ar-**H**) and 7.39-7.46 (1H, m, Ar-**H**);

LCMS retention time ~ 2.62 min, m/z (FIAPOSES) 325.0 [Cl^{35} $(M+H)^+$, 100%] and 327.0 [Cl^{37} $(M+H)^+$, 33%].

Example 54

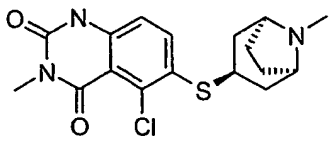
EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazole-2-thione



To a stirred solution EXO-6-Amino-2-chloro-3-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenol hydrochloride salt (Example 16 (iii), 250mg, 0.84mmol) and triethylamine (338mg, 3.4mmol) in $CHCl_3$ (30cm^3) was added a solution of thiophosgene (115mg, 1.00mmol) as a solution in $CHCl_3$ (3cm^3). After stirring at room temperature for one hour the reaction was loaded onto a 10g SCX-2 cartridge, washed with methanol then extracted using methanolic ammonia (~2N). The basic eluant was concentrated *in vacuo* to a brown solid which was washed with $CHCl_3$ (2 x 5cm^3) and methanol (2 x 2cm^3) to yield EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazole-2-thione (136mg, 48%) as a pale brown solid; δ_H (300MHz; D6 DMSO) 1.79-1.99 (6H, m, 6 x one of CH_2), 2.14-2.19 (2H, m, 2 x one of CH_2), 2.53 (3H, s, NCH_3), 3.28-3.50 (1H, m, HCS), 3.72-3.86 (2H, m, 2 x NCH), 6.92-7.0 (1H, m, Ar-H) and 7.20-7.28 (1H, m, Ar-H); LCMS retention time ~ 2.83 min, m/z (FIAPOSES) 341.0 [Cl^{35} $(M+H)^+$, 100%] and 343.0 [Cl^{37} $(M+H)^+$, 33%].

Example 55

EXO-5-Chloro-3-methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinazoline-2,4-dione

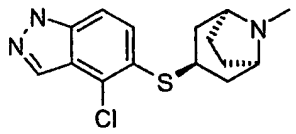


By proceeding in a similar manner to Example 41 but using N-methyl-2,3-dichlorobenzene-carboxamide in step (i) and omitting step (iv), there was prepared the

title compound as a colourless solid. δ_H (300MHz; $CDCl_3$) 1.52-1.61 (2H, m, 2 x one of CH_2), 1.69-1.91 (4H, m, 4 x one of CH_2), 1.99-2.09 (2H, m, 2 x one of CH_2), 2.25 (3H, s, $CHNCH_3$), 3.17-3.22 (2H, m, 2 x NCH), 3.30-3.49 (4H, m, $CONCH_3$ and SCH), 7.84-6.92 (1H, m, Ar-H) and 7.61-7.70 (1H, m, Ar-H); LCMS retention time ~ 1.37 min, m/z (FIAPOSES) 366.1 [Cl^{35} $(M+H)^+$, 100%] and 368.1 [Cl^{37} $(M+H)^+$, 33%].

Example 56

EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole



(i) 1,2-Dichloro-3-methyl-4-nitro-benzene

The title compound was prepared according to the procedure described in patent application EP 0778 258 A2 (Example 1). The crude mixture of products and starting material was purified using Flash Chromatography on silica (eluant = hexane). Yielding a 10:1 mixture of 1,2-Dichloro-3-methyl-4-nitro-benzene {δ_H (300MHz; $CDCl_3$) 7.41-7.50 (1H, m, Ar-H) and 7.65-7.71 (1H, m, Ar-H); LCMC retention ~6.42min} and 2,3-Dichloro-1-methyl-4-nitro-benzene {δ_H (300MHz; $CDCl_3$) 8.01-8.08 (1H, m, Ar-H) and 8.17-8.21 (1H, m, Ar-H); LCMC retention ~6.57min} as a waxy solid.

(ii) EXO-3-(2-Chloro-3-methyl-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane

To a stirred solution of 1,2-Dichloro-3-methyl-4-nitro-benzene (300mg, 1.45mmol) and EXO-Thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl) ester (376mg, 1.89mmol) in ethanol was added 2N NaOH (~2cm^3) at room temperature under a flow of nitrogen gas. The reaction was stirred at room temperature overnight then treated with 2N HCl (2cm^3) to reach pH~5 then concentrated *in vacuo* onto silica and columned using gradient elution (98:2 to 85:15 CH_2Cl_2:methanolic ammonia) yielding EXO-3-(2-Chloro-3-methyl-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane (~150mg) as a crystalline solid; δ_H (300MHz; $CDCl_3$) 1.62-1.71 (2H, m, 2 x one of CH_2), 1.87-1.97 (4H, m, 4 x one

of CH_2), 2.09-2.19 (2H, m, 2 x one of CH_2), 2.31 (3H, s, CH_3), 2.60 (3H, s, CH_3), 3.21-3.28 (2H, m, 2 x NC**H**), 3.50-3.61 (1H, m SC**H**), 7.12-7.20 (1H, m, Ar-**H**) and 7.70-7.79 (1H, m, Ar-**H**); LCMC retention ~3.56min, m/z (FIAPOS) 327.1 [Cl^{35} $(M+H)^+$, 100%] and 329.1 [Cl^{37} $(M+H)^+$, 33%].

(iii) EXO-3-Chloro-2-methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine

To a slurry of 5%Pd on charcoal (145mg) and ethanol was added a solution of EXO-3-(2-Chloro-3-methyl-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane (145mg, 0.44mmol) in ethanol. This mixture was placed under a pressurised atmosphere of hydrogen gas (60 PSI) at room temperature for 90 minutes. The reaction was filtered through celite® then concentrated *in vacuo* to yield EXO-3-Chloro-2-methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine (77mg); δ_H (300MHz; $CDCl_3$) 1.50-1.59 (2H, m, 2 x one of CH_2), 1.60-1.71 (2H, m, 2 x one of CH_2), 1.73-189 (2H, m, 2 x one of CH_2), 1.93-2.01 (2H, m, 2 x one of CH_2), 2.24 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.14-3.31 (3H, m, SC**H** and 2 x NC**H**), 6.47-6.54 (1H, m, Ar-**H**) and 7.16-7.22 (1H, m, Ar-**H**);

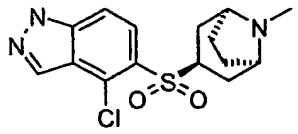
(iv) EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole

To a stirred solution EXO-3-Chloro-2-methyl-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine (1.1g, 3.7mmol) in $HBF_{4(aq)}$ (48% solution in H_2O) (2.5cm^3) was added $NaNO_2$ (256mg, 3.7mmol) as a solution in H_2O at room temperature. The reaction changed colour from orange/yellow to blue/green. After one hour the reaction was filtered to yield a sticky pale green solid which was washed with water then $CHCl_3$ and then dried *in vacuo*. This solid was treated with $CHCl_3$ and 18-crown-6 ether (catalytic amount) and then Potassium acetate (727mg, 7.4mmol) was added causing a colour change from green to reddish orange with a sticky insoluble gum. The solution was purified using Flash chromatography {gradient elution (98:2 to 85:15 CH_2Cl_2:methanolic ammonia)} yielding EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole (510mg) as a reddish brown dry foam; δ_H (300MHz; $CDCl_3$) 1.56-1.70 (2H, m, 2 x one of CH_2), 1.72-2.10 (6H, m, 6 x one of CH_2), 2.22 (3H, s, NCH_3), 3.18-3.40 (3H, m, **H**CS and 2 x NC**H**), 7.11-7.20 (1H, m, Ar-**H**), 7.41-7.50 (1H, m, Ar-**H**) and 8.08

(1H, s, Ar-**H**); LCMS retention time ~ 2.38 min, m/z (FIAPOSES) 308.1 [Cl^{35} $(M+H)^+$, 100%] and 310.1 [Cl^{37} $(M+H)^+$, 33%].

Example 57

EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-1*H*-indazole

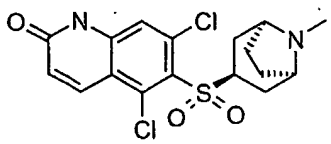


To a cloudy slurry of EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-indazole (Example 19, 393mg, 1.28mmol) in methanol (18cm^3) with a small amount of $CHCl_3$ (2cm^3) to try and aid solvation, was added a solution of Oxone (1.57g, 2.56mmol) at room temperature causing instant formation of a white solid. After stirring for one hour the reaction was loaded onto a SCX-2 cartridge and washed with methanol, then the cartridge was extracted with methanolic ammonia (~2N). The basic solution was concentrated *in vacua* to yield EXO-4-Chloro-5-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-1*H*-indazole (420mg) as a brown foam; δ_H (300MHz $CDCl_3$) 1.51-1.71 (4H, m, 4 x one of CH_2), 2.02-2.19 (4H, m, 4 x one of CH_2), 2.31 (3H, s, NCH_3), 3.29-3.35 (2H, m, 2 x NCH), 3.71-3.89 (1H, m, HCS), 7.40-7.48 (1H, m, Ar-H), 7.90-7.99 (1H, m, Ar-H) and 8.25 (1H, s, Ar-H); LCMS retention time ~ 1.69min, (FIAPOSES) 340.0 [Cl^{35} $(M+H)^+$, 100%], 342.0 [Cl^{37} $(M+H)^+$, 33%].

By proceeding in a similar manner there were prepared the following:

Example 58

EXO 5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-1*H*-quinolin-2-one

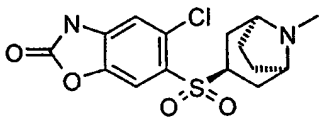


δ_H (300MHz; D4 methanol) 1.78-1.99 (4H, m, 4 x one of CH_2), 2.28-2.49 (4H, m, 4 x one of CH_2), 2.53 (3H, s, NCH_3), 4.10-4.25 (1H, m, HCS), 6.99-7.08 (1H, m, Ar-**H**), 8.11

(1H, s, Ar-H) and 8.61-8.69 (1H, m, Ar-H); LCMS retention time ~ 0.64 min, m/z (FIAPOSES). 401.0 [Cl^{35} + Cl^{35} $(M+H)^+$, 100%] and 403.0 [Cl^{35} + Cl^{37} $(M+H)^+$, 67%].

Example 59

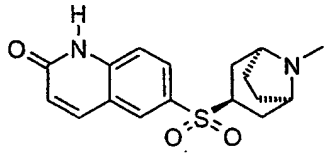
EXO-5-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-3*H*-benzooxazol-2-one



δ_H (300MHz; D6 DMSO) 1.45-1.59 (4H, m, 4 x one of CH_2), 1.80-2.00 (4H, m, 4 x one of CH_2), 2.26 (3H, s, NCH_3), 3.64-3.79 (1H, m, SCH), 6.92 (1H, s, Ar-H) and 7.28 (1H, s, Ar-H);

Example 60

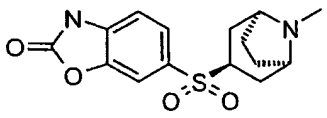
EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-1*H*-quinolin-2-one



δ_H (300MHz; D4 Methanol) 1.69-1.89 (4H, m, 4 x one of CH_2), 2.00-2.20 (4H, m, 4 x one of CH_2), 2.40 (3H, s, NCH_3), 3.45-3.55 (2H, m, 2 x NCH), 3.56-3.67 (1H, m, HCS), 6.71-6.79 (1H, m, Ar-H), 7.51-7.58 (1H, m, Ar-H), 7.95-8.02 (1H, m, Ar-H), 8.08-8.13 (1H, m, Ar-H) and 8.22-8.24 (1H, m, Ar-H).

Example 61

EXO 6-(8-Methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-3*H*-benzooxazol-2-one

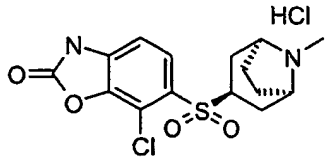


δ_H (300MHz; D6 DMSO) 1.50-1.63 (4H, m, 4 x one of CH_2), 1.72-1.85 (2H, m, 2 x one of CH_2), 1.88-1.99 (2H, m, 2 x one of CH_2), 2.22 (3H, s, NCH_3), 3.29-3.39 (2H, m, 2 x

NCH), 7.11-7.20 (1H, m, Ar-H) and 7.47-7.58 (2H, m, 2 x Ar-H); LCMS retention time ~0.95 min, m/z (FIAPOS) 323.1 [$(M+H)^+$, 100%].

Example 62

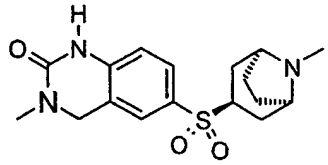
EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-3*H*-benzooxazol-2-one hydrochloride salt



EXO-7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]octane-3-sulfonyl)-3*H*-benzooxazol-2-one hydrochloride salt; δ_H (300MHz; D4 methanol) 1.81-1.99 (4H, m, 4 x one of CH_2), 2.10-2.30 (4H, m, 4 x one of CH_2), 2.61 (3H, s, NCH_3), 3.74-4.00 (3H, m, HCS and 2 x NCH), 7.22-7.36 (1H, m, Ar-H) and 7.70-7.80 (1H, m, Ar-H).

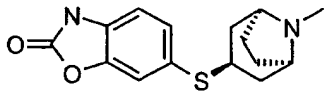
Example 63

EXO-3-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfonyl)-1*H*,3*H*,4*H*-tetrahydroquinazolin-2-one



Example 64

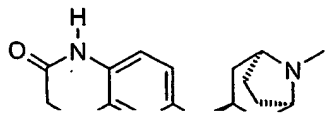
EXO-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one



By proceeding in a similar manner to Example 44 but using 3*H*-benzooxazol-2-one in place of 2-hydroxyquinoline, there was prepared the title compound as a colourless solid.

Example 65

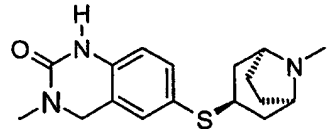
EXO-6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*,3*H*,4*H*-tetrahydroquinolin-2-one



By proceeding in a similar manner to Example 43 but using 1*H*,3*H*,4*H*-tetrahydroquinolin-2-one in place of 2-hydroxyquinoline, there was prepared the title compound as a pale yellow solid.

Example 66

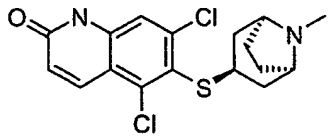
EXO-3-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*,3*H*,4*H*-tetrahydroquinazolin-2-one



By proceeding in a similar manner to Example 44 but using 3-methyl-1*H*,3*H*,4*H*-tetrahydroquinazolin-2-one in place of 2-hydroxyquinoline, there was prepared the title compound as a pale yellow solid.

Example 67

(a) EXO-5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one



(i) EXO-3-(2,6-Dichloro-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane

To a pale brown solution of EXO-Thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl) ester (3.93g, 19.7mmol) and 1,2,3-Trichloro-5-nitro-benzene (5.37g, 23.7mmol) in ethanol was added 2 NaOH (10.85cm^3, 21.7mmol) at room temperature. After about five minutes the reaction was neutralised using 2N HCl (~1cm^3) then concentrated *in vacuo* to remove the ethanol. The aqueous was treated with 2N NaOH (1.5cm^3) and extracted using $CHCl_3$ (2 x 100cm^3), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo* to dark yellow oil. This oil was purified by Flash Chromatography on silica (95:5 to 85:15; CH_2Cl_2,methanolic ammonia) yielding EXO- 3-(2,6-Dichloro-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane (5.12g, 83%) as long yellow crystals

{δ_H (300MHz; $CDCl_3$) 1.47-1.70 (4H, m, 4 x one of CH_2), 1.87-2.05 (4H, m, 4 x one of CH_2), 2.30 (3H, s, NCH_3), 3.11-3.20 (2H, m, 2 x NCH), 3.60-3.73 (1H, m SCH) and 8.23 (2H, m, 2 x Ar-H).

(ii) EXO-3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine To a slurry of 5%Pd on charcoal (2g) and ethanol was added a solution of EXO- 3-(2,6-Dichloro-4-nitro-phenylsulfanyl)-8-methyl-8-aza-bicyclo[3.2.1]octane (5.12g, 14.8mmol) in ethanol. This mixture was placed under a pressurised atmosphere of hydrogen gas (60 PSI) at room temperature overnight. The reaction was filtered through celite® then concentrated *in vacuo* to give a colourless oil which was triturated with diethyl ether then concentrated *in vacuo* to yield EXO-3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine (4.33g, 93%) as a dry white foam; δ_H (300MHz; $CDCl_3$); 1.47-1.70 (4H, m, 4 x one of CH_2), 1.82-2.03 (4H, m, 4 x one of CH_2), 2.29 (3H, s, NCH_3), 3.11-3.21 (2H, m, 2 x NCH), 3.22-3.39 (1H, m SCH), 3.81-3.92 (NH_2) and 6.70 (2H, s, 2 x Ar-H); LCMC retention ~1.70min, m/z (FIAPOS) 317.1 [Cl^{35} + Cl^{35} $(M+H)^+$, 100%] and 319.1 [Cl^{35} + Cl^{37} $(M+H)^+$, 66%].

(iii) EXO-*N*-[3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenyl]-3-ethoxy-acrylamide

To a solution of EXO-3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenylamine (300mg, 0.95mmol) in pyridine ($1cm^3$) and CH_2Cl_2 ($10cm^3$) was added 3-Ethoxy-acryloyl chloride (127mg, 0.95mmol) which was synthesised from ethoxy-ethene according to a literature procedure (Fernandez, Franco; Garcia-Mera, Xerardo; Morales, Melvin; Rodriguez-Borges, Jose E.; Synthesis; 2; 2001; 239-242). The reaction was stirred at room temperature for 2.5 hours then the solid that had formed was filtered off and washed with CH_2Cl_2 to yield EXO-*N*-[3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenyl]-3-ethoxy-acrylamide hydrochloride salt (289mg, ~68%); δ_H (300MHz; D4 methaol) 1.30-1.41 (3H, m, OCH_2CH_3), 1.90-2.18 (6H, m, 6 x one of CH_2), 2.23-2.47 (2H, m, 2 x one of CH_2), 2.76 (3H, s, NCH_3), 3.48-3.52 (1H, m, SCH), 3.81-3.90 (2H, m, 2 x NCH), 3.92-4.01 (2H, m, OCH_2CH_3), 5.55-5.65 (2H, m, NH and C=CH), 7.59-7.69 (1H, m, C=CH) and 7.81-7.86 (2H, m, 2 x Ar-H); LCMC retention

~2.38min, m/z (FIAPOS) 415.1 [Cl^{35} + Cl^{35} $(M+H)^+$, 100%] and 417.1 [Cl^{35} + Cl^{37} $(M+H)^+$, 66%].

(iv) EXO-5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one hydrochloride salt

EXO-*N*-[3,5-Dichloro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-phenyl]-3-ethoxy-acrylamide hydrochloride salt (280mg) was treated with concentrated H_2SO_4 (~1cm^3) causing a colour change from yellow to red. After 10 minutes the reaction was poured onto crushed ice. This was slowly warmed to room temperature to give a yellow solution which was basified using 2N NaOH (~10cm^3) to give a turbid mixture which was extracted with $CHCl_3$ (2 x 30cm^3). The chloroform layer was treated with methanol, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow solid. This yellow solid was washed with CH_2Cl_2 then dissolved in methanol and treated with methanolic HCl to yield EXO-5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one hydrochloride salt (100mg) as a white solid; δ_H (300MHz; $CDCl_3$) 1.95-2.36 (8H, m, 4 x CH_2), 2.78 (3H, s, NCH_3), 3.53-3.70 (1H, m, HCS), 3.89-3.99 (2H, m, 2 x NCH), 6.71-6.79 (1H, m, Ar-H), 7.52 (1H, s, Ar-H) and 8.28-8.33 (1H, m, Ar-H); LCMS retention time ~ 1.65 min, m/z (FIAPOSES) 369.1 [Cl^{35} + Cl^{35} $(M+H)^+$, 100%] and 371.1 [Cl^{35} + Cl^{37} $(M+H)^+$, 67%].

(b) EXO-5-chloro-8-methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one

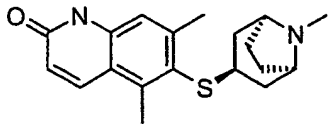
By proceeding in a similar manner to Example 67(a) but using 4,5-dichloro-2-nitro-toluene in step (i), there was prepared EXO-5-chloro-8-methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one.

(c) EXO-5,7-dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-1*H*-quinolin-2-one

By proceeding in a similar manner to Example 67(a) but using exo-thioacetic acid *S*-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl) ester [Example 42(ii)] in step (i), there was prepared EXO-5,7-dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-ylsulfanyl)-1*H*-quinolin-2-one.

Example 68

EXO-5,7-Dimethyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one

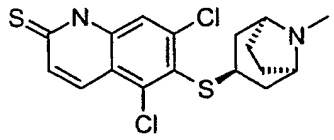


By proceeding in a similar manner to Example 67 but using 1-chloro-2,6-dimethyl-4-nitro-benzene in place of 1,2,3-trichloro-5-nitro-benzene, there was prepared the title compound as a colourless solid.

δ_H (300MHz $CDCl_3$) 1.39-1.48 (2H, m, 2 x one of CH_2), 1.54-1.63 (2H, m, 2 x one of CH_2), 1.79-2.00 (4H, m, 4 x one of CH_2), 2.25 (3H, s, NCH_3), 2.61 (CH_3), 2.82 (CH_3), 2.91-3.08 (1H, m, HCS), 3.09-3.16 (2H, m, 2 x NCH), 6.65-6.71 (1H, m, Ar-H), 7.20 (1H, s, Ar-H), 7.97-8.05 (1H, m, Ar-H) and 12.32 (1H, br s, NH); LCMS retention time ~ 2.93min, (FIAPOSES). 329.1 [$(M+H)^+$, 100%].

Example 69

EXO 5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinoline-2-thione

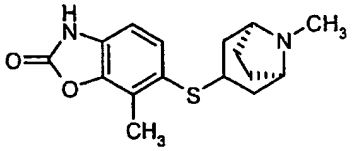


A slurry EXO-5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinolin-2-one (407mg, 1.1mmol) and Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (446mg, 1.10mmol) in toluene was heated to reflux under a flow of nitrogen gas overnight. The reaction was cooled to room temperature then concentrated *in vacuo* onto silica and columned using gradient elution (98:2 to 75:25 CH_2Cl_2:methanolic ammonia) yielding EXO-5,7-Dichloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-1*H*-quinoline-2-thione (160mg) as a bright yellow solid; δ_H (300MHz $CDCl_3$) 1.47-1.55 (2H, m, 2 x one of CH_2), 1.60-1.71 (2H, m, 2 x one of CH_2), 1.89-2.01 (4H, m, 4 x one of CH_2), 2.29 (3H, s, NCH_3), 3.13-3.21 (2H, m, 2 x

NCH), 3.38-3.41 (1H, m, HCS), 7.39-7.47 (2H, m, 2 x Ar-H) and 7.91-7.99 (1H, m, Ar-H).

Example 70

EXO-7-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one



(i) 7-Methyl-3*H*-benzooxazol-2-one-6-sulfonic acid

7-Methyl-3*H*-benzooxazol-2-one [5.0g, 33 mmol, prepared according to the procedure described in J. Org. Chem. (1982), 47(14), 2804-6] was treated with chlorosulphonic acid as described in Example 15 (i) to give the title compound as an off- white solid (4.5g, 60%).

δ_H (300MHz, DMSO) 2.50 (s, 3H), 6.83 (d, 1H), 7.58 (d, 1H), 11.60 (brs, 1H)

(ii) EXO-7-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylsulfanyl)-3*H*-benzooxazol-2-one

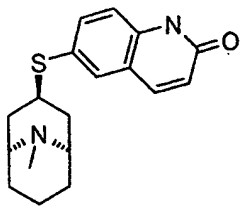
A mixture of 7-methyl-3*H*-benzooxazol-2-one-6-sulfonic acid (2.5g, 11 mmol), triphenylphosphine (13g, 50 mmol) and benzene (100 mL) was heated at reflux for 2h under Dean and Stark conditions. The reaction was cooled and treated with iodine (5g, 20 mmol) in small portions. The reaction was heated to reflux for a further 48h before being cooled and washed with 2.0M aqueous sodium hydroxide (2 X 20 ml). The combined aqueous extracts were washed with chloroform (2 X 50ml) and acidified to pH 4 with concentrated hydrochloric acid. The resultant solid was collected and dried to yield a white solid which was used directly in the next step.

This material was treated with ENDO-methanesulfonic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester and cesium fluoride in DMF according to the procedure described in Example 15 (iii). There was thus obtained the title compound as a colourless solid.

δ_H (300MHz; D4 methanol) 1.82-2.26 (8H), 2.65 (3H, s), 2.78 (3H, s), 3.35-3.49 (1H, m), 3.72-3.83 (2H, m), 6.96 (1H, d) and 7.40 (1H, d). FIA-MS: 305 [$(M+H)^+$, 100%].

Example 71

6-(9-Methyl-9-aza-bicyclo[3.3.1]non-3 *(exo)*-ylsulfanyl)-1-*NH*-quinolin-2-one



(i) 9-Methyl-9-aza-bicyclo[3,3,1]nonan-3*(endo)*-ol

To a –78°C cooled solution of pseudopelletierine (771 mg, 5.04 mmol), obtained from the its chloro hydrate (pseudopelletierine chloride, commercially available) by treatment with saturated aqueous solution of $NaHCO_3$, extracted with methylene chloride, and dried; in THF anhydrous (20 mL), a solution 1.0 M of DIBAL-H in hexane or toluene (10.8 mL, 10.8mmol) was added dropwise under N_2. The mixture was stirred and allowed to reach rt. for 3h. The reaction was quenched with water (2mL) and poured into diethyl ether (60 mL). $NaHCO_3$ anhydrous (20 g) and Na_2SO_4 anhydrous (20 g) were added. The mixture was stirred for 2h at rt., and then, it was filtered and the filtrate was evaporated. The residue was the title compound pure, 684 mg, 88%.

Ion Electrospray Mass Spectrum M+1: 156.

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.16 (m, 1 H), 2.95 (br m, 2 H), 2.40-2.20 (m, 2 H), 2.00-1.80 (m, 3 H), 1.40-1.25 (m, 3 H), 1.20-1.05 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 62.9, 51.6, 40.4, 34.8, 24.9, 14.4

(ii) 3*(endo)*-Hydroxy-9-aza-bicyclo[3,3,1]nonane-9-carboxylic acid ethyl ester

To a solution of the intermediate from step (i) (2.31 g, 14.90 mmol) in dry chloroform (300 mL), ethyl chloroformate (9.97 mL, 104.30 mmol) followed by potassium bicarbonate (1.78 g, 17.88 mmol) were added. The mixture was heated at 80°C and stirred under N_2 overnight. The reaction was cooled down, quenched with water (30 mL) and extracted with chloroform. The organic layer was dried on $MgSO_4$ anhydrous, and the solvent was removed in vacuo. The residue was the title compound pure, 3.04g, 96%. The product is a mixture of rotamers, the major one is described as following:

Ion Electrospray Mass Spectrum M+1: 214

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.45 (br d, 2 H), 4.10 (q, J = 7.0 Hz, 2H), 3.68 (m, 1 H), 2.30 (m, 2 H), 1.84 (br, s, 1 H), 1.50-1.30 (m, 7 H), 1.23 (t, J = 7.0 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 154.2, 62.8, 60.1, 43.9, 33.5, 29.3, 13.7, 13.0

(iii) 3*(endo)*-Methanesulfonyloxy-9-aza-bicyclo[3,3,1]nonane-9-carboxylic acid ethyl ester

To an ice-cooled solution of the intermediate from step (ii) (3.04 g, 14.27 mmol) in methylene chloride anhydrous, pyridine anhydrous (1.04 mL, 12.84 mmol) followed by methanesulfonate chloride (1.21 mL, 15.70 mmol) were added under N_2. The mixture was stirred overnight and allowed to reach rt. As the reaction hadn't finished pyridine anhydrous (2.08 mL, 26 mmol) and methanesulfonate chloride (2.42 mL, 31.40 mmol) were added at 0°C under N_2. The new mixture was stirred at rt for 24h. The reaction was quenched with an aqueous solution of NH_4OH (32%), and extracted with methylene chloride. The organic layer was washed with brine and dried on $MgSO_4$ anh. The solvent was removed in vacuo to give the title compound, 1.34 g, 32%. The product is a mixture of rotamers, the major one is described as following
Ion Electrospray Mass Spectrum M+1: 292
^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.66 (m, 1 H), 4.50 (br m, 2 H), 4.10 (q, J = 7.0 Hz, 2H), 2.99 (s, 3 H), 2.45 (m, 2 H), 1.70-1.50 (m, 8 H), 1.24 (t, J = 7.0Hz, 3H)

(iv) 3*(exo)*-(2-Oxo-1,2-dihydro-quinolin-6-ylsulfanyl)-9-aza-bicyclo[3.3.1]nonane-9-carboxylic acid ethyl ester

To a solution of the intermediate from step (iii) (1.34 g, 4.60 mmol), thioacetic acid *S*-(2-oxo-1,2-dihydro-quinolin-6-yl) ester (98.3 mg, 0.78 mmol), cesium fluoride (699 mg, 4.60mmol) in dry DMF (10 mL), pyrrolidine (654.3 mg, 9.20 mmol) was added at rt. The mixture was degassed, heated at 80°C and stirred overnight under N_2. The reaction was quenched with water, and filtered to remove the cessium fluoride excess. The filtrate was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried on $MgSO_4$ anh. The solvent was removed in vacuo to give the title compound, which was submitted to the next reaction without further treatment.
Ion Electrospray Mass Spectrum M+1: 373, M-1: 371.

(v) 6-(9-Methyl-9-aza-bicyclo[3.3.1]non-3 *(exo)*-ylsulfanyl)-1-*NH*-quinolin-2-one

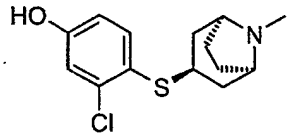
To an ice-cooled solution of the intermediate from step (iv) (536 mg, 1.4 mmol) in toluene anhydrous (11 mL), sodium bis(methoxyethoxy) aluminium hydride (Red-Al (3.4 M in toluene)) (1.47mL, 5.02mmol) was added. The mixture was stirred overnight under N_2 and allowed to reach rt. Once the starting material had disappeared by mass analysis, the solvent was removed in vacuo. The residue was dissolved in methanol and submitted to SCX purification followed by SPE purification. As the desired product was further purified by reverse phase HPLC in two batches. For the first batch, formic acid was used in the purification and 50 mg, 10%, were obtained of the title compound. From the second one, trifluoroacetic acid was used getting 70 mg, 12% of the corresponding trifluorooacetate salt. Total yield: 22%

Ion Electrospray Mass Spectrum M+1: 315 .

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) for the free amine: 7.96 (d, J = 9.5 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.70 (dd, J = 8.5 y 1.9 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 9.5 Hz, 1H), 3.92 (m, 1H), 3.54 (br, s, 2H), 2.90 (s, 3H), 2.24 (m, 6H), 2.04 (m, 1H). 1.92 (m, 2H), 1.73 (m, 1H)

Example 72

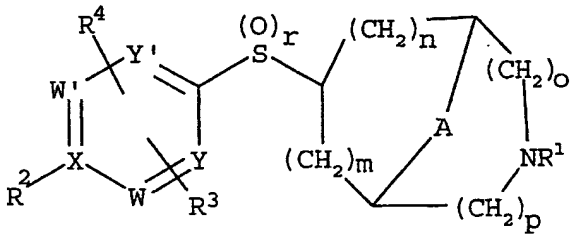
3-Chloro-4-[(8-methyl-8-azabicylo[3.2.1]oct-3-yl)thio]phenol



By proceeding in a similar manner to Example 9 but using 3-chlorophenol in place of 3-bromophenol in step (i), there was prepared the title compound as a colourless solid. δ_H (300MHz; D6 DMSO) 1.47 (2H, m), 1.58 (4H, m), 1.90 (2H, m), 2.10 (3H, s), 3.02 (2H, m), 3.28 (1H, m), 6.75 (1H, m), 6.90 (1H, m); 7.39 (1H, m); FIA-MS: 284[$(M+H)^+$, 100%].

Claims:

1. A compound represented by Formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is -H,

-OH,

$-NH_2$,

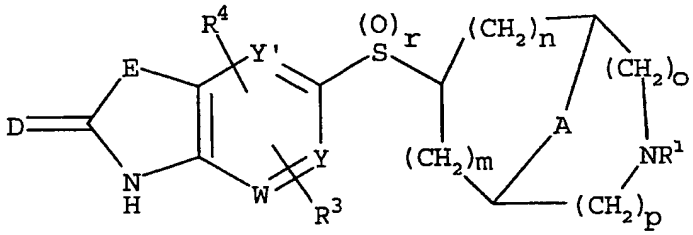
-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or $-SO_2$-;
V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -$C(O)OC_{1-4}$alkyl, -$OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and
T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent,

aryl,

-$(L)_a$-Z, wherein L is CH_2, CO, O, NH or N(C_{1-4}alkyl) and a is 0 or 1;
and

Z is C_{1-3}alkyl-F, C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{0-3}alkyl-SO_2-R^6, C_{0-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6, C_{1-3}alkyl-CN or C_{1-3}alkyl-NR^6_2, wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)

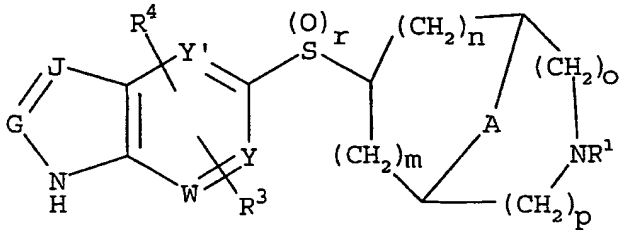


(Ia)

wherein D is O or S; and

E is O, S, NR^5, $C(R^5)_2$, O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-O, CR^5_2-$S(O)_r$, CR^5_2-NR^5, CR^5_2-CR^5_2, CO-NR^5, or CR^5=CR^5; or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib)



Formula (Ib)

wherein G is CR^5 or N; and

J is CR^5 or N;

unless X is N in which case R^2 is absent

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

R^6 is each independently H, C_{1-6}alkyl, aryl or arylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms;

X is C or N;

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m, n, o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

provided that

when X, W, W', Y and Y' are all C, R^3 is H, R^4 is H or Cl positioned *meta* to the sulphur atom, A is $(CH_2)_q$ and R^1 is selected from H, unsubstituted C_{1-4}alkyl and unsubstituted C_{3-4}cycloalkyl; then R^2 may not be H or –OH,

and that

when one of X, Y and Y' is N, R^3 is H, R^4 is H or Cl positioned *meta* to the sulphur atom, A is $(CH_2)_q$ and R^1 is selected from H, unsubstituted C_{1-4}alkyl and unsubstituted C_{3-4}cycloalkyl; then R^2 may not be H or –OH.

2. A compound as claimed in Claim 1

wherein:

R^2 is -H,

$-NH_2$,

-NH-Q-V-T as defined in claim 1,

aryl,

$-(L)_a$-Z as defined in claim 1,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;

unless X is N in which case R^2 is absent.

3. A compound as claimed in Claim 1 or Claim 2

wherein:

R^2 is -NH-Q-V-T as defined in claim 1,

aryl,

$-(L)_a$-Z as defined in claim 1,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;

unless X is N in which case R^2 is absent.

4. A compound as claimed in any one of Claims 1 to 3

wherein:

R^2 is -NH-Q-V-T wherein Q is -C(O)-NH-, or -C(O)O-;

V is as defined in claim 1; and

T is as defined in claim 1;

aryl,

$-(L)_a$-Z as defined in claim 1,

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia) as defined in claim 1, or

linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib) as defined in claim 1;

unless X is N in which case R^2 is absent.

5. A compound as claimed in Claim 1

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is -H,

-OH,

$-NH_2$,

-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or $-SO_2-$;

V is aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -C(O)OC_{1-4}alkyl, -OC(O)C_{1-4}alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and

T is H, halogen, aryl, aryl-C_{1-4}alkyl, or aryloxy,

unless X is N in which case R^2 is absent

R^3 is H, halogen, C_{1-4}alkyl, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, or -C_{1-4}alkyl-OH,

R^4 is H, halogen, C_{1-4}alkyl, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, $-SO_2NH_2$, $-SO_2NHC_{1-4}$alkyl, or -C_{1-4}alkyl-OH,

X is C or N,

W is C or N, provided that both X and Y are not N,

W' is C

Y is C or N

Y' is C

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$,

m, n, o and p are independently 0, 1, 2 or 3

q is optionally 1, 2 or 3

r is 0.

6. A compound as claimed in claim 5 wherein R^1 is H, C_{1-6}alkyl optionally substituted with 1 or 2 hydroxyl groups, or aryl-C_{1-4}alkyl.

7. A compound as claimed in claim 6 wherein R^1 is benzyl, p-methoxybenzyl, furanylmethyl, imidazolylmethyl, pyridinylmethyl, thienylmethyl, pyridylmethyl, N-hydroxypyridylmethyl or thiazolylmethyl.

8. A compound as claimed in any one of claims 5 to 7 wherein R^2 is H, R^3 is carbonamido (-$CONH_2$) or C_{1-4}alkyl-OH, and R^4 is H, C_{1-4}alkyl, CF_3, halogen or cyano.

9. A compound as claimed in any one of claims 5 to 7 wherein R^2 is OH, and R^3 and R^4 each independently represent H, C_{1-4}alkyl, CF_3, cyano or halogen.

10. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-Q-V-T; T is H and R^3 and R^4 each independently represent H, methyl, CF_3, chloro- or cyano-.

11. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-SO_2-V-T; V is aryl, -C_{1-12}alkyl or aryl-C_{1-12}alkyl; R_3 is H, methyl, CF_3, Cl or cyano and R^4 is H.

12. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-SO_2-V-T, V is selected from C_{1-12}alkyl, phenyl, naphthyl, thienyl, oxazolyl, isoxazolyl, or phenyl(CH=CH)–, optionally substituted with 1, 2, 3 or 4 substituents selected from:

-NO_2;

halogen;

$-CF_3$;

C_{1-12}alkoxy;

C_{1-12}alkylthio;

C_{1-12}alkyl;

C_{1-4}alkylsulfonyl;

-CN;

$-OCF_3$;

$-C(O)OC_{1-4}$alkyl;

$-OCH_2CF_3$;

$-NHC(O)C_{1-4}$alkyl.

13. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – $NH-SO_2-V-T$, T is selected from H; or diazole, oxazole, isoxazole, phenyl or phenoxy, optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;

halogen;

$-CF_3$;

C_{1-12}alkoxy;

C_{1-12}alkylthio;

C_{1-12}alkyl;

C_{1-4}alkylsulfonyl;

-CN;

$-OCF_3$;

$-C(O)OC_{1-4}$alkyl;

$-OCH_2CF_3$;

$-NHC(O)C_{1-4}$alkyl.

14. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – $NH-SO_2-V-T$, V is selected from 3-chloro-4-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, naphthyl, 2,4,6-trimethylphenyl, phenyl(CH=CH)-, 4-chlorophenyl, 2-chlorophenyl, 2,5-dichlorothien-3-

yl, 2,5,6-trimethyl-4-methoxyphenyl, 4-methoxyphenyl, 2,3,4-trifluorophenyl, 3-cyanophenyl, 2-methoxycarbonylthien-3-yl or 4-pentylphenyl and T is H.

15. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-SO_2-V-T, T is 2-chloro-5-nitrophenoxy and V is phenyl.

16. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-C(O)-V-T wherein V is selected from aryl; aryl-C_{1-12}alkyl; diaryl-C_{1-12}alkyl; lactonyl; or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy or aryloxy.

17. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-C(O)-V-T, and V is selected from C_{1-12}alkyl, phenyl, phenyl-C_{1-12}alkyl, diphenylmethyl, naphthyl, furanyl, thienyl, diazolyl, pyridinyl, thiazolyl, benzothienyl, fluorenyl, oxazolyl or isoxazolyl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkoxy;
C_{1-12}alkylthio;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl;
$-OCH_2CF_3$.

18. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-C(O)-V-T, T is selected from H; halogen; or diazole, oxazole, isoxazole, phenyl, phenoxy or benzodioxanyl optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkylthio;
C_{1-12}alkoxy;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl.

19. A compound as claimed in any one of Claims 5 to 7 wherein R^2 is of formula – NH-C(O)NH-V-T wherein V is selected from C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy or aryloxy; aryl; or aryl-C_{1-12}alkyl.

20. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-C(O)NH-V-T, V is selected from phenyl, phenyl-C_{1-12}alkyl or naphthyl optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkylthio;
C_{1-12}alkoxy;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl.

21. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula – NH-C(O)O-V-T, wherein V is selected from C_{1-18}alkyl optionally substituted with

halogen, hydroxyl, C_{1-4}alkoxy, $C(O)OC_{1-4}$alkyl, $OC(O)C_{1-4}$ alkyl, aryl-C_{1-4}alkoxy or aryloxy; aryl; or aryl-C_{1-12}alkyl.

22. A compound as claimed in any one of claims 5 to 7 wherein R^2 is of formula –NH-C(O)O-V-T, preferably V is selected from phenyl or phenyl-C_{1-12}alkyl optionally substituted with 1, 2, 3 or 4 substituents selected from

$-NO_2$;
halogen;
$-CF_3$;
C_{1-12}alkylthio;
C_{1-12}alkoxy;
C_{1-12}alkyl;
C_{1-4}alkylsulfonyl;
-CN;
$-OCF_3$;
$-C(O)O-C_{1-4}$alkyl; or
$-OCH_2CF_3$.

23. A compound as claimed in claim 1 wherein R^2 is of formula –NH-C(O)-V-T
wherein V is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl or aryl-C_{1-12}alkyl; and
T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent.

24. A compound as claimed in claim 23
wherein V is H, C_{1-6}alkyl or C_{3-6}cycloalkyl; and
T is H unless V is H in which case T is absent.

25. A compound as claimed in claim 23
wherein V is aryl or aryl-C_{1-12}alkyl; and
T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy.

26. A compound as claimed in claim 25

wherein V is phenyl, pyridyl, thienyl, thiazolyl, thiadiazolyl, or phenyl-C_{1-6}alkyl;

and

T is H, halogen, C_{1-5}alkyl, C_{1-4}alkoxy, nitro, aryl, aryl-C_{1-4}alkyl, or aryloxy.

27. A compound as claimed in claim 1

wherein

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is -NH_2, or

-NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or -SO_2-;
V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -C(O)OC_{1-4}alkyl, -OC(O)C_{1-4}alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and
T is H, halogen, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

X is C;

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are not more than two N atoms in the aryl ring and provided that at least one of W, W', Y or Y' is N;

A is optionally a CH=CH double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

28. A compound as claimed in claim 27 wherein

W is C;

W' is C;

Y' is C; and

Y is N.

29. A compound as claimed in claim 27 wherein

W is N;

W' is C;

Y' is C; and

Y is C.

30. A compound as claimed in any one of claims 27 to 29 wherein

R^2 is $-NH_2$.

31. A compound as claimed in any one of claims 27 to 29 wherein

R^2 is -NH-Q-V-T, wherein Q is -C(O)-, -C(O)-NH-, -C(O)O-, or $-SO_2-$;

V is H, aryl, aryl-C_{1-12}alkyl, diaryl-C_{1-12}alkyl, lactonyl, or C_{1-18}alkyl optionally substituted with halogen, hydroxyl, C_{1-4}alkoxy, -

$C(O)OC_{1-4}$alkyl, $-OC(O)C_{1-4}$alkyl, aryl-C_{1-4}alkoxy, aryloxy, or SO_2C_{1-4}alkyl; and
T is H, halogen, aryl, aryl-C_{1-4}alkyl, or aryloxy unless V is H in which case T is absent.

32. A compound as claimed in claim 31 wherein

Q is $-SO_2-$ or –CO-.

33. A compound as claimed in claim 1 wherein

R^1 is -H,
C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is aryl,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or-C_{1-4}alkyl-OH,

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

X is C,

W is C or N;

W' is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a CH=CH double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

34. A compound as claimed in claim 33 wherein R^2 is a C_3 to C_{12} aromatic or heteroaromatic group optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

35. A compound as claimed in claim 33 wherein R^2 is phenyl, naphthyl, fluorenyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl or carbolinyl optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

36. A compound as claimed in claim 33 wherein R^2 is phenyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothienyl, or quinolinyl, optionally substituted with one or more substituents selected from C_{1-12}alkyl, C_{1-12}alkoxy, thio, C_{1-12}alkylthio, carboxy, carboxy(C_{1-6}alkyl), formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonylalkoxy, nitro, trihalomethyl, trihaloalkoxy, trihalomethoxy, trihalomethyl(C_{1-6}alkyl), hydroxy, hydroxy(C_{1-6})alkyl, (C_{1-6}alkoxy)carbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminocarboxy, C_{1-6}alkylaminocarboxy, di(C_{1-6}alkyl)aminocarboxy, aminocarboxy(C_{1-6})alkyl, C_{1-6}alkylaminocarboxy(C_{1-6}alkyl), di(C_{1-6}alkyl)aminocarboxy(C_{1-6}alkyl), C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonyl(C_{1-6}alkyl)amino, halo, C_{1-6}alkylhalo, sulphamoyl, tetrazolyl and cyano.

37. A compound as claimed in claim 1

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is $(L)_a$-Z, wherein L is O, CO, CH_2, NH or N(C_{1-4}alkyl) and a is 0 or 1; and

Z is C_{1-3}alkyl-F, C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{0-3}alkyl-SO_2-R^6, C_{0-3}alkyl-SO_2-NR^6_2, C_{1-3}alkyl-OR^6, C_{1-3}alkyl-CN or C_{1-3}alkyl-NR^6_2 wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^6 is each independently H, C_{1-6}alkyl, aryl, or arylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms;

X is C;

W is C or N,

Y is C or N,

W' is C or N,

Y' is C or N,

provided that there are no more than two N atoms in the aryl ring,

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

38. A compound as claimed in claim 37 wherein L is O, CO or CH_2.

39. A compound as claimed in claim 37 wherein L is NH or N(C_{1-4}alkyl).

40. A compound as claimed in any one of claims 37 to 39 wherein Z is C_{0-3}alkyl-aryl-R^6, C_{0-3}alkyl-CO-NR^6_2, C_{0-3}alkyl-CO_2-R^6, C_{1-3}alkyl-OR^6 or C_{1-3}alkyl-NR^6_2 wherein each C_{0-3}alkyl or C_{1-3}alkyl portion is optionally substituted with from 1 to 6 groups selected from F and C_{1-5}alkyl.

41. A compound as claimed in any one of claims 37 to 40 wherein Z is C_{0-3}alkyl-aryl-R^6 wherein aryl is selected from phenyl, naphthyl, fluorenyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, diazolyl, triazolyl, tetrazolyl, benzothiazolyl, benzimidazolyl, pyrrolinyl, imidazolinyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, oxyindolyl, isoindolyl, indazolyl,

indolinyl, 7-azaindolyl, azabenzimidazolyl, carbazolyl benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzodioxolyl, benzodioxanyl, cinnolinyl or carbolinyl optionally, be substituted with one or more substituents selected from C_1 to C_{12} alkyl (preferably C_1 to C_6 alkyl), C_1 to C_{12} alkoxy (preferably C_1 to C_6 alkoxy), thio, C_1 to C_{12} alkylthio (preferably C_1 to C_6 alkylthio), carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, trihalo(C_1 to C_6 alkoxy), trihalomethoxy, trihalomethyl(C_1 to C_6 alkyl), hydroxy, hydroxy(C_1 to C_6)alkyl, (C_1 to C_6 alkoxy)carbonyl, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aminocarboxy, C_1 to C_6 alkylaminocarboxy, di(C_1 to C_6 alkyl)aminocarboxy, aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylaminocarboxy(C_1 to C_6)alkyl, di(C_1 to C_6 alkyl)aminocarboxy(C_1 to C_6)alkyl, C_1 to C_6 alkylcarbonylamino, C_1 to C_6 alkylcarbonyl(C_1 to C_6 alkyl)amino, halo, C_1 to C_6 alkylhalo, sulphamoyl, tetrazolyl and cyano and wherein each C_{0-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

42. A compound as claimed in any one of claims 37 to 40 wherein Z is C_{1-3}alkyl-CO-NR^6_2, wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

43. A compound as claimed in any one of claims 37 to 40 wherein Z is C_{1-3}alkyl-CO_2-R^6, wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

44. A compound as claimed in any one of claims 37 to 40 wherein Z is C_{1-3}alkyl-OR^6 wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

45. A compound as claimed in any one of claims 37 to 40 wherein Z is C_{1-3}alkyl-NR^6_2 wherein each C_{1-3}alkyl portion is optionally substituted with from 1 to 3 groups selected from F and C_{1-3}alkyl.

46. A compound as claimed in any one of claims 37 to 45 wherein R^6 is/are each independently H, C_{1-6}alkyl, phenyl, or phenylC_{1-4}alkyl, each of which (except H) may be optionally substituted with from 1 to 3 fluorine atoms.

47. A compound as claimed in any one of claims 37 to 46 wherein R^6 is/are each independently H, methyl, ethyl, propyl, cyclohexyl, or benzyl, each of which (except H) may be optionally substituted with 1, 2 or 3 fluorine atoms.

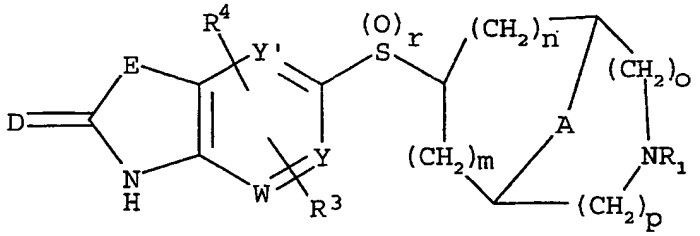
48. A compound as claimed in Claim 1

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



(Ia)

wherein D is O or S; and

E is O, S, NR^5, or $C(R^5)_2$,

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-}

$_{10}$cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring,

A is optionally a double bond, $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

49. A compound as claimed in Claim 48 wherein E is O or NR^5.

50. A compound as claimed in Claim 48 or 49 wherein R^5 is/are each independently H or C_{1-4}alkyl.

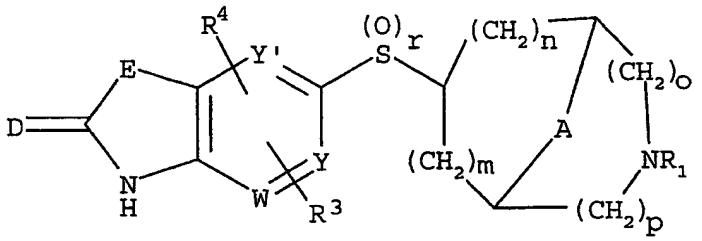
51. A compound as claimed in Claim 1

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ia)



(Ia)

wherein D is O or S; and

E is O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-O, CR^5_2-$S(O)_r$, CR^5_2-NR^5, CR^5_2-CR^5_2, CO-NR^5, or CR^5=CR^5;

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H, C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N;

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond or $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

52. A compound as claimed in Claim 51 wherein E is O-CR^5_2, NR^5-CR^5_2, NR^5-CO, CR^5_2-CR^5_2, or CR^5=CR^5.

53. A compound as claimed in Claim 51 or 52 wherein E is O-CR^5_2, NR^5-CO, or CR^5=CR^5.

54. A compound as claimed in any one of Claims 51 to 53 wherein R^5 is/are each independently H or C_{1-4}alkyl.

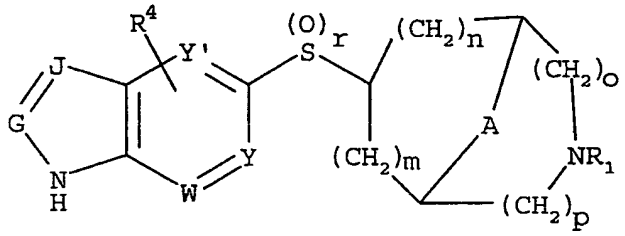
55. A compound as claimed in Claim 1

wherein:

R^1 is -H,

C_{1-12}alkyl optionally substituted with 1, 2 or 3 groups independently selected from halogen, hydroxyl, thiol, C_{1-4}alkoxy or C_{1-4}alkylthio, or aryl-C_{1-4}alkyl;

R^2 is linked back to the aromatic ring so as to form a fused bicyclic compound represented by Formula (Ib)



Formula (Ib)

wherein G is CR^5 or N; and

J is CR^5 or N;

R^3 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^4 is H, halogen, C_{1-4}alkyl optionally substituted with from 1 to 3 fluorine atoms, cyano, CF_3, OC_{1-4}alkyl, aryloxy, arylC_{1-4}alkyl, arylC_{1-4}alkoxy, C_{3-10}cycloalkoxy, carboxy, carbonamido, -CO-NH-C_{1-4}alkyl, aryl, hydroxy, -SO_2NH_2, -SO_2NHC_{1-4}alkyl, or -C_{1-4}alkyl-OH;

R^5 is each independently H or C_{1-4}alkyl;

X is C;

W is C or N;

Y is C or N;

Y' is C or N

provided that there are no more than two N atoms in the aryl ring;

A is optionally a double bond or $(CH_2)_q$ or $(CH_2)O(CH_2)$;

m,n,o and p are independently 0, 1, 2 or 3;

q is optionally 1, 2 or 3;

r is 0, 1 or 2.

56. A compound as claimed in Claim 5 wherein each R^5 is H.

57. A compound as claimed in Claim 1 or any one of claims 23 to 56 wherein r is 0.

58. A compound as claimed in Claim 1 or any one of claims 23 to 56 wherein r is 2.

59. A compound as claimed in any one of Claims 1 to 6 or 8 to 58 wherein R^1 is H or C_{1-3}alkyl, preferably methyl.

60. A compound as claimed in any preceding claim wherein A is CH_2, CH_2CH_2 or CH=CH.

61. A compound as claimed in any preceding claim wherein m and n are 1 or 2 and o and p are 0 or 1.

62. A compound as claimed in any preceding claim wherein m and n are 1 and o and p are 0.

63. A compound as claimed in any preceding claim wherein m and n are 1, o and p are 0 and A is CH_2CH_2 or CH=CH.

64. A compound as claimed in any preceding claim wherein

R^3 is H, halogen, C_{1-4}alkyl, CF_3, or OC_{1-4}alkyl, and

R^4 is H, halogen, C_{1-4}alkyl, CF_3, or OC_{1-4}alkyl.

65. A compound as claimed in any preceding claim wherein one or both of R^3 and R^4 are positioned ortho to the $S(O)_r$ moeity.

66. A pharmaceutical composition comprising a compound as claimed in any preceding claim with a pharmaceutically acceptable diluent or carrier.

67. A compound as claimed in any one of claims 1 to 65 or a composition as claimed in claim 66 for use in therapy.

68. Use of a compound as claimed in any one of claims 1 to 65 for the manufacture of a medicament for the treatment of a condition indicating treatment with a beta 4 subtype selective nicotinic acetylcholine receptor modulator.

69. A method of treatment of a condition indicating treatment with a beta 4 subtype selective nicotinic acetylcholine receptor modulator comprising administering an effective amount of a compound as claimed in any one of claims 1 to 65 or a composition as claimed in claim 66 to a patient in need thereof.

70. Use of a compound as claimed in any one of claims 1 to 65 for the manufacture of a medicament for the treatment of dysfunctions of the central and autonomic nervous systems.

71. A method of treatment of dysfunctions of the central and autonomic nervous systems comprising administering an effective amount of a compound as claimed in any one of claims 1 to 65 or a composition as claimed in claim 63 to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 02/21296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D451/04 C07D451/14 A61K31/55 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 99 32117 A (SIBIA NEUROSCIENCES INC ;VERNIER JEAN MICHEL (US); MC DONALD IAN A) 1 July 1999 (1999-07-01) cited in the application page 4, line 13 -page 5, line 18; claim 1	1-71
Y	WO 97 19059 A (SIBIA NEUROSCIENCES INC ;VERNIER JEAN MICHEL (US); MCDONALD IAN A) 29 May 1997 (1997-05-29) cited in the application page 2, line 15 -page 3, line 16; claim 1	1-71
X	WO 96 37226 A (MENNITI FRANK S ;PFIZER (US); CHENARD BERTRAND L (US)) 28 November 1996 (1996-11-28) preparations 36,38, 39 and 41	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2002	21/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Wörth, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19817 A (ABBOTT LAB) 22 March 2001 (2001-03-22) claim 1	1-71
Y	WO 00 44755 A (ABBOTT LAB) 3 August 2000 (2000-08-03) claim 1	1-71
Y	ELLIOT R L ET AL: "2-(ARYLOXYMETHYL) AZACYCLIC ANALOGUES AS NOVEL NICOTINIC ACETYLCHOLINE RECEPTOR (NACHR) LIGANDS" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 19, 1996, pages 2283-2288, XP000618280 ISSN: 0960-894X table 1	1-71
A	RADL, STANISLAV ET AL: "Synthesis and analgesic activity of some side-chain modified anpirtoline derivatives" ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) (2000), 333(5), 107-112 , XP002219143 compounds of formula 4a and 4b	1
A	KRAISS, G. ET AL: "Stereospecific methods of forming ethers by nucleophilic reactions of 3.alpha.-substituted tropanes" J. ORG. CHEM. (1968), 33(6), 2601-3 , XP002219144 experimental section "tropane-3-phenyl thioether"	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-71 (all part)

subject-matter related to monocyclic aromatic compounds

2. Claims: 1-71 (all part)

subject-matter related to bicyclic compounds of formulae (Ia) and (Ib)

The present subject-matter relates to compounds comprising an aza-bicyclic portion and an aromatic portion linked via an optionally oxidized sulphur atom that modulate neurotransmission by promoting the release of neurotransmitters such as acetylcholine.

However, document WO-A-9932117 already discloses compounds falling within the present scope having the same pharmacological activity comprising a monocyclic heteroaromatic part.

Furthermore, document WO-A-9719059 discloses in table II a neurotransmitter releasing compound comprising a monocyclic aromatic part.

The Applicant introduced therefore a proviso in claim 1 which excludes some subject-matter of the said prior art.

However, since the disclaimed compounds have the same pharmacological activity, the remaining scope of the claims does not contain a special technical feature which defines a contribution over the prior art.

Consequently, there is no technical relationship among the claimed compounds apparent representing a single inventive concept.

The subject-matter of the present international application can therefore be divided in at least two groups of inventions mentioned above.

However, in view of the disclosure of documents WO-A-9719059 and WO-A-9932177, the first group of inventions (compounds comprising a monocyclic aromatic portion) represents itself multiple groups of inventions inter alia dependent on the nature of substituent R2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/21296

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 69 and 71 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte d Application No
PCT/US 02/21296

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9932117	A	01-07-1999	AU	748991 B2	13-06-2002
			AU	1943799 A	12-07-1999
			CA	2315941 A1	01-07-1999
			EP	1043999 A1	18-10-2000
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WO 0044755	A	03-08-2000	AU	2856900 A	18-08-2000
			BG	105836 A	29-03-2002
			BR	0007664 A	07-05-2002
			CN	1345320 T	17-04-2002
			CZ	20012716 A3	14-11-2001
			EP	1147112 A1	24-10-2001
			HU	0200332 A2	29-06-2002
			NO	20013731 A	18-09-2001
			SK	10692001 A3	07-01-2002
			TR	200102162 T2	21-12-2001
			WO	0044755 A1	03-08-2000